

MEMORANDUM

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FROM: George Alexeeff, Ph.D.
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DATE: March 24, 1998

SUBJECT: 1,4-Dioxane Action Level

SUMMARY

In response to your request to Office of Environmental Health Hazard Assessment (OEHHA), dated December 16, 1997, for OEHHA concurrence for the Action Level of 3 ppb (parts per billion) for 1,4-dioxane (CAS Registry number 123-91-1) proposed by Department of Health Services (DHS) based on the U.S. EPA (1997) cancer potency listed on Integrated Risk Information System (IRIS), we have reviewed the latest OEHHA (1989) document and recent publications of the relevant toxicological and regulatory review literature (ACGIH 1991, ATSDR 1996, HSDB 1997, RTECS 1997, TOMES 1998, U.S.EPA 1997) and summarized the findings below. Our analysis shows that we concur with DHS and U.S. EPA on the public-health protective concentration of 0.003 mg/L (3 ppb).

BACKGROUND

1,4-Dioxane (C₄H₈O₂), also called dioxane, dioxan, p-dioxane, diethylene dioxide, diethylene oxide, diethylene ether or glycol ethylene ether, is a synthetic industrial solvent used mainly as a stabilizer in chlorinated solvents. It is an ingredient in paints, varnishes, detergents, cements, stains, inks, cosmetics and is a natural component in vine-ripped tomatoes and tomato products, fresh shrimps, brewed coffee and fried chicken. Dioxane has been detected at concentrations of 1 - 220,000 ppb in groundwater, 1 - 290 ppb in surface water and 0.1 - 2,100 ppb in drinking water (ATSDR 1996, HSDB 1997).

1,4-Dioxane is a volatile, flammable, colorless liquid with a mild ether-like odor at room temperature. It is miscible with water and highly mobile in soils rapidly migrating to groundwater. It is a dangerous fire and explosion hazard when exposed to heat or flame, and reacts vigorously with oxidizing materials. Dioxane is stable when dry, but becomes unstable at elevated temperatures and pressures. It produces explosive peroxides in the presence of moisture under certain conditions (Sax 1988, HSDB, 1997). The odor threshold is reported to be 12 ppm (NJHSFS 1997) or 24 ppm (ACGIH 1991). Limited data suggest that 1,4-dioxane will not bioaccumulate in fish or food chains. It is resistant to microbial degradation.

Inhalation is the most common route of human exposure to 1,4-dioxane. It is readily adsorbed through the lungs, skin and gastrointestinal tract of mammals. Distribution is rapid and uniform in lung, liver, kidney, spleen, colon and skeletal muscle tissue. The percentage of covalent binding is highest in the liver, spleen and colon in the rats. Dioxane is mostly excreted as 2-hydroxyethoxyacetic acid (HEAA) in expired air through the lungs, and HEAA and p-dioxane-2-one in the urine.

An enforceable Maximum Contaminant Level (MCL) has not been established for 1,4-dioxane in drinking water. The U.S. EPA (1997) issued a one-day Health Advisory (HA) of 4,000 ppb for a child, a ten-day HA for a child of 400 ppb and a drinking water concentration of 3 ppb at 10^{-6} cancer risk level. The state drinking water guideline for dioxane is 2 ppb in Michigan, 7 ppb in North Carolina, 20 ppb in Connecticut, 30 ppb in Minnesota, 50 ppb in Massachusetts and 70 ppb in Maine (HSDB 1997).

HEALTH EFFECTS

There are no data regarding the health effects of human exposure via the oral route. Human systemic effects, including fatalities with liver and kidneys as the chiefly affected organs, have been reported in workers repeatedly exposed to low concentrations by inhalation. Acute toxic effects of 1,4-dioxane through inhalation in animal studies include eye, nose and throat irritation and kidney and liver damages. Some reproductive and developmental effects have been observed in laboratory rodents following inhalation exposure to high concentrations of 1,4-dioxane. Toxic responses to 1,4-dioxane through dermal exposure in humans have not been reported.

1,4-Dioxane has low acute toxicity by the oral route for cat, rabbit, guinea pig, rat and mouse. It is an irritant to eye, nose, lung, mucous membrane and skin. The oral LD_{50} of 1,4-dioxane is about 2 g/kg in rabbits and adult cats, 3.15 - 4 g/kg in guinea pigs, 5.7 - 5.9 g/kg in mice and 5.4 - 7.3 g/kg in rats. The intraperitoneal LD_{50} is 0.799 g/kg in rats and 0.79 g/kg in mice (ACGIH 1991, Sax 1994). The inhalation LC_{50} for a two-hour exposure period is approximately 37 g/m³ in mice and 46 g/m³

in rats, and for a four-hour exposure in female rats is about 14,250 ppm (~ 4 g/m³). The dermal LD₅₀ is about 7.6 g/kg in rabbits (RTECS 1997). At these doses regardless the route of exposure, signs of anesthesia and narcosis with gastric, hepatic and renal lesions often preceded death (ATSDR 1996). In the subchronic and chronic studies, kidneys and liver are targeted organs for toxicity of 1,4-dioxane.

1,4-Dioxane has caused cancers in animals. It is classified as a group B2 probable human carcinogen by the U.S. EPA (1997). IARC (1987) also lists it as a group 2B carcinogen, which is possibly carcinogenic to humans. ATSDR (1996) recently concurred with the U.S. EPA that 1,4-dioxane is a weak genotoxic carcinogen and a strong promoter. 1,4-Dioxane administered in drinking water induced liver and nasal cavity tumors in rats, liver carcinomas and adenomas in mice, and liver and gall bladder tumors in guinea pigs. Reticular cell sarcomas were found in rats exposed to dioxane through inhalation. It has also been shown to be a promoter in a two-stage skin carcinogenesis study in mice (OEHHA 1989).

1,4-Dioxane appears to be only weakly genotoxic in a sister chromatid exchange assay without (but not with) enzyme activation in cultured Chinese hamster ovary cells. With and without exogenous metabolic activation, 1,4-Dioxane tested negative in *Salmonella typhimurium*, *Saccharomyces cerevisiae*, *Escherichia coli*, *Photobacterium phosphoreum*, *Drosophila melanogaster*, in vitro mouse lymphoma and chromosomal aberration assays. Inconclusive results were noted for micronuclei induction. No oncogenicity information on dioxane in humans has been found in the literature (ATSDR 1996).

CALCULATION OF THE CANCER POTENCY

Under the mandates of Proposition 65, OEHHA (1989) reviewed toxicological data and developed risk-specific intake levels based on animal carcinogenicity. For this purpose, OEHHA selected the cancer potency [q_1^* (human)] of 0.027 (mg/kg/day)⁻¹ calculated for the combined incidence of hepatocellular adenomas and carcinomas in female B6C3F1 mice in the NCI (1978) study for 1,4-dioxane. At that time, an interspecies scaling factor of a 2/3 power as shown in the first equation below (U.S. EPA 1986) was used instead of the currently recommended (U.S. EPA 1992, 1996) power of 3/4 as shown in the second equation below.

$$q_1^*_{(\text{human})} = q_1^*_{(\text{animal})} \times (\text{animal lifespan/experimental duration})^3 \times (\text{human body weight/animal body weight})^{1/3}$$

$$q_1^*_{(\text{human})} = q_1^*_{(\text{animal})} \times (\text{animal lifespan/experimental duration})^3 \times (\text{human body weight/animal body weight})^{1/4}$$

The OEHHA (1989) selected cancer potency [q_1^* (human)] of $0.027 \text{ (mg/kg/day)}^{-1}$ was derived using the above first equation as shown below:

$$\begin{aligned} q_1^* \text{ (human)} &= \frac{[0.0014 \text{ (mg/kg/day)}^{-1}] \times (104 \text{ weeks}/90 \text{ weeks})^3}{\times (70 \text{ kg}/0.035 \text{ kg})^{1/3}} \\ &= 0.027 \text{ (mg/kg/day)}^{-1} \end{aligned}$$

Using the second equation, a new cancer potency [q_1^* (human)] of $0.014 \text{ (mg/kg/day)}^{-1}$ can be derived as below:

$$\begin{aligned} q_1^* \text{ (human)} &= \frac{[0.0014 \text{ (mg/kg/day)}^{-1}] \times (104 \text{ weeks}/90 \text{ weeks})^3}{\times (70 \text{ kg}/0.035 \text{ kg})^{1/4}} \\ &= 0.014 \text{ (mg/kg/day)}^{-1} \\ &= 1.4 \times 10^{-2} \text{ (mg/kg-day)}^{-1} \end{aligned}$$

The drinking water study by NCI (1978) has also been selected to serve as the basis for calculating the cancer potency [q_1^* (human)] listed on IRIS by the U.S. EPA (1997). A cancer potency of $0.011 \text{ (mg/kg/day)}^{-1}$ calculated for the incidence of squamous cell carcinoma of the nasal turbinates in male Osborne-Mendel rats was listed on the IRIS database.

CALCULATION OF THE ACTION LEVEL

For carcinogens, the following general equation can be used to calculate the public health-protective concentration (C) for a chemical in drinking water (in mg/L):

$$C = \frac{BW \times R}{q_1^* \text{ (human)} \times L/\text{day}} = \text{mg/L}$$

where,

- BW = Adult body weight
- R = De minimis level for lifetime excess individual cancer risk
- q_1^* (human) = Cancer slope factor, q_1^* (human) is the upper 95% confidence limit multistage animal
- L/day = Daily volume of water consumed by an adult.

A public-health protective concentration for carcinogenic effects of 1,4-dioxane based on a carcinogenic potency of $1.4 \times 10^{-2} \text{ (mg/kg-day)}^{-1}$ derived above can be calculated using the following values:

$$BW = 70 \text{ kg (The default adult male human body weight)}$$

$$\begin{aligned} R &= 10^{-6} \text{ (Default de minimis lifetime excess individual cancer risk)} \\ q_1^{*}(\text{human}) &= 1.4 \times 10^{-2} \text{ (mg/kg-day)}^{-1} \text{ (cancer slope factor estimated as above)} \\ L/\text{day} &= 2 \text{ L/day (The default daily water consumption).} \end{aligned}$$

Thus,

$$C = \frac{70 \times 10^{-6}}{(1.4 \times 10^{-2}) \times 2} = 2.5 \times 10^{-3} \text{ mg/L} = 3 \text{ } \mu\text{g/L (rounded).}$$

The calculated public-health protective concentration for 1,4-dioxane in drinking water is rounded up to 3 ppb or 3 $\mu\text{g/L}$.

Using the U.S. EPA IRIS (1997) cancer potency of $0.011 \text{ (mg/kg/day)}^{-1}$ from the same study, the concentration is derived as follows:

$$C = \frac{70 \times 10^{-6}}{(1.1 \times 10^{-2}) \times 2} = 3.2 \times 10^{-3} \text{ mg/L} = 3 \text{ } \mu\text{g/L (rounded).}$$

The corresponding drinking water concentration for 1,4-dioxane is also rounded to 3 ppb or 3 $\mu\text{g/L}$. The DHS proposed Action Level based on the U.S. EPA selected cancer potency is 3 ppb.

CONCLUSIONS

The present analysis calculates a public-health protective concentration of 3 ppb with many of the same assumptions used in the OEHHA (1989) document and is consistent with the calculated value based on the U.S. EPA (1997) IRIS database for health advisories for 1,4-dioxane as shown above. Please note that this public-health protective concentration of 3 ppb is for ingestion of drinking water only and does not take into account potential dermal and inhalation exposures resulting from typical household uses of water containing 1,4-dioxane. Therefore OEHHA concurs with the DHS proposal of an Action Level of 3 ppb for 1,4-dioxane.

If you have any questions or need further assistance, please feel free to call Dr. Anna Fan at (510)-540-3066.

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