Public Health Goal for 2,4-DICHLOROPHENOXYACETIC ACID in Drinking Water

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**2,4-DICHLOROPHENOXYACETIC ACID** ii December 1997
in Drinking Water
California Public Health Goal (PHG)
PREFACE

Drinking Water Public Health Goal of the
Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the
information used by DHS for establishing drinking water standards. PHGs established by OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.
SUMMARY

A Public Health Goal (PHG) of 70 ppb is developed for 2,4-dichlorophenoxyacetic acid (2,4-D) in drinking water. This report provides a brief discussion of the herbicide 2,4-D and its amine, esters and salts to support the determination of our PHG of 70 ppb based on a no-observed-adverse-effect level (NOAEL) of 1 mg/kg-day for hematologic, renal and liver effects in 90-day and chronic rat studies. This PHG is identical to the current state Maximum Contaminant Level (MCL), established in 1994 on the basis of the Recommended Public Health Level (RPHL) of 70 ppb proposed by the Office of Environmental Health Hazard Assessment (OEHHA) in 1991. This level is also consistent with the U.S. Environmental Protection Agency’s (U.S. EPA’s) MCL and MCL Goal (MCLG) of 70 ppb set in 1991. Therefore, OEHHA adopts a PHG of 0.07 mg/L (70 ppb) for 2,4-D in drinking water.

INTRODUCTION

For this review, the medical literature was searched with Medline and several hundred citations were retrieved. Titles and abstracts (if present) were scanned to identify research relevant to an update of the previous regulatory value. Articles which appeared to have the potential to affect the regulatory level were retrieved. Among these, the most significant animal studies are new acute, subchronic and chronic toxicity studies (Charles et al., 1996a,b; Paulino et al., 1996). The report on chronic tests by Charles et al. (1996a) provides new cancer bioassays in rats and mice. These studies were conducted by Dow Chemical Company at the request of U.S. EPA to investigate doses of 2,4-D higher than in the previous studies (Dow, 1983).

TOXICOLOGY

The report on chronic tests by Charles et al. (1996a) provides new cancer bioassays in rats and mice. These studies were conducted by the Dow Chemical Company. The previous observation of astrocytomas in male rats at 45 mg/kg-day (Dow, 1983) was not confirmed in the present study at doses of 5, 75 and 150 mg/kg-day for two years. There were no increased tumor rates in either male or female rats, although cataracts and retinal degeneration were found in both male and female rats at 150 mg/kg-day. There was also no increase in tumor rates in mice administered 2,4-D in food for two years at 5, 150 or 300 mg/kg-day for females and 5, 62.5 or 125 mg/kg-day for males. In both rats and mice, a chronic NOAEL of 5 mg/kg was determined for 2,4-D acid added to food.

In the Paulino et al. (1996) study, male rats were exposed to 200 ppm of 2,4-D dimethylamine salt in their drinking water for 180 days, which provided an equivalent daily dose of about 20 to 25 mg/kg. Modest changes observed in serum enzymes suggest some liver and muscle cytotoxicity, but no macroscopic or histopathological lesions were observed at autopsy. These results are also consistent with the new acute and subchronic studies in rats carried out by Dow (Charles et al., 1996b), which showed modest hematological, kidney and liver effects at the low doses, with an NOAEL of 15 mg/kg-day. Cataracts and retinal degeneration were found in 300 mg/kg-day female rats.
Another Dow Chemical Company study on subchronic effects of 2,4-D in dogs (Charles et al., 1996c) compared the toxicity of 2,4-D free acid, its dimethylamine salt and its 2-ethylhexyl ester over 90 days of administration in the feed (four beagle dogs/sex/group at 0, 1.0, 3.75 or 7.5 mg/kg-day, plus an extra 0.5 mg/kg-day dose for the free acid; all doses calculated as free acid equivalents). The three chemical forms appeared to be toxicologically equivalent. The “overall NOAEL” for the three chemicals is stated by the authors to be 1.0 mg/kg, although some moderate effects were observed on serum parameters (increased alanine aminotransferase and creatinine) at 1 mg/kg, which were not considered to be biologically significant. The NOAEL for adverse liver effects observed by histology was 3.75 mg/kg for each chemical. The paper also reports on a one-year chronic administration of the free acid in feed to five dogs/sex/dose at 1, 5 or 7.5 mg/kg-day. Body weight gains were decreased at all doses but were only significantly decreased at 5 and 7.5 mg/kg-day, except for one time period at 1 mg/kg-day in females. The NOAEL for the most sensitive effects in this one-year study was 1 mg/kg-day for both sexes for liver inflammation and changes in several clinical chemistry parameters.

Multiple epidemiological investigations have suggested an association of herbicide use or potential exposure with various tumor types. However, the tumor types increased have been inconsistent among studies. The several studies indicated a possible increase in non-Hodgkin’s lymphoma and soft tissue sarcomas associated with agricultural applications of phenoxyacetic acid herbicides (Hoar et al., 1986; Kelly and Guidotti, 1989; Zahm et al., 1990). Davis et al. (1993) found increased brain cancer among children was strongly associated (odds ratios up to 6.2) with household use of pesticides, including 2,4-D, the herbicide most widely used around homes. Leiss and Savitz (1995) found odds ratios of about four for treatment of yards with pesticides among children aged 0 to 14 with soft tissue sarcomas, compared to case-controls. This analysis was conducted on a database of childhood cancer cases in the Denver metropolitan area from 1976 to 1983 collected for an electromagnetic field exposure study. Actual number of cases are small (24 cases, 216 controls) and the stated odds ratios cannot be readily derived from the values provided in the paper. Attempts to communicate with the authors to substantiate the calculations have been unsuccessful. All of these studies are complicated by exposures to multiple chemicals, especially 2,4,5-T and its contaminant, 2,3,7,8-TCDD. It should be noted that the registration of the active ingredient 2,4,5-T has now been canceled, and TCDD is claimed not to be a contaminant of 2,4-D.

Garry et al. (1996) recently conducted an extensive analysis of birth defects among offspring of pesticide “appliers” in Minnesota. This analysis shows a positive correlation of birth anomalies and altered sex ratio of births with increased regional use of chlorphenoxy herbicides and fungicides for births between 1989 and 1992. To quote the abstract, “The pattern of excess frequency of birth anomalies by pesticide use, season and alteration of sex ratio suggests exposure-related effects in [pesticide] applicators and the general population of the crop-growing region of western Minnesota.” This is consistent with earlier studies which show various abnormal health outcomes to be increased in rural areas compared to urban areas, and vice-versa, but does not clearly point to specific causes of the differences.

Association of a variety of tumors and reproductive disruption with overall use of pesticides is likely to show correlation with the most frequently used pesticide types, such as chlorphenoxy herbicides. This does not prove a cause and effect relationship. The inconsistency among the various studies as to tumor types increased may reflect multiple competing risk factors or, perhaps, chance association with 2,4-D. However, even if the adverse health effects are due to 2,4-D, it
would be impossible at present to use these data for quantitative risk assessment, because of the lack of any exposure measures. Due to this uncertainty, and the lack of evidence for carcinogenicity, mutagenicity or any low-dose reproductive effects of 2,4-D, the PHG must be calculated from the noncarcinogenic systemic effects in animals. Therefore, the PHG is based on an effective chronic NOAEL of 1 mg/kg-day in both rats and dogs (Dow, 1983; Charles et al., 1996c).

OTHER REGULATORY STANDARDS

U.S. EPA’s MCL and MCLG of 70 ppb were derived from an NOAEL of 1 mg/kg-day based on hematologic, renal and liver effects at 5 mg/kg-day in 90-day and chronic rat studies (Dow, 1983). These studies were summarized and published by Munro et al. (1992). The MCL and MCLG were derived from this NOAEL using an uncertainty factor of 100, assuming that an adult drinks two liters of water per day and that drinking water contributes 20% (0.2) of the total exposure (U.S. EPA, 1991). The MCL of 70 ppb is expressed as the concentration of the free 2,4-D acid. The free acid is relatively quickly formed in the environment by hydrolysis of the ester and amine forms, so the toxicity of the different 2,4-D products is considered equivalent (on a free-acid basis) for setting public health protective levels in drinking water. U.S. EPA’s MCL is identical to the current State MCL, established in 1994 on the basis of OEHHA’s RPHL of 70 ppb (OEHHA, 1991).

CALCULATION OF PHG

Calculation of a public health-protective concentration (C, in mg/L) for 2,4-D is based on the general equation for noncarcinogenic endpoints:

$$C = \frac{\text{NOAEL} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{L/day}} = \text{mg/L}$$

where,

- NOAEL = No-observed-adverse-effect level (1 mg/kg-day)
- BW = Body weight for an adult male (70 kg)
- RSC = Relative source contribution of 20% (0.2)
- UF = Uncertainty factor of 100 (10-fold for interspecies variation and 10-fold for human variability)
- L/day = Volume of daily drinking water consumption for an adult (2 L/day).

For the calculation of a public health-protective concentration, an NOAEL of 1 mg/kg-day is selected from a chronic rat study (Dow, 1983) and from subchronic and chronic studies in dogs (Charles et al., 1996c). An uncertainty factor (UF) of 100 is applied to account for interspecies extrapolation and probable variability among humans. This is intended to allow for potential sensitive individuals or populations, including infants and children. These uncertainty factors are consistent with the latest U.S. EPA practices, which more specifically acknowledge actual uncertainty in data extrapolations. No synergistic interactions with other chemicals are known or expected.
There are two exposure measures in these equations, the relative source contribution (RSC) and the water consumption rate (L/day). The RSC is based on an estimate of the contribution of drinking water relative to other sources of exposure to the chemical contaminant. The other sources are food, air, soil contact, occupational exposures and exposure through smoking. Often food is the most significant source of exposure in addition to drinking water exposure. U.S. EPA’s RSC range is 20% to 80%, depending on the available data. OEHHA and U.S. EPA use an RSC of 20%, reflecting the assumption that drinking water makes up 20% of the exposure to the chemical unless data or relevant information are available to support an alternative value.

For the widely-used herbicide 2,4-D, there should be widespread dietary exposures to trace levels of the chemical in crops, although it has a relatively short environmental half-life and does not bioaccumulate in soil, plants or animals. Pesticide tolerances for 2,4-D are generally less than 1 ppm in edible portions of food, and actual detected residues average much lower (HSDB, 1996). Exposures to 2,4-D in air should be low-level and infrequent for the general population, caused mostly from overspray during application of the product to lawns for weed control. The RSC from drinking water will therefore be set at 20%, based on exposure to trace levels of 2,4-D in both air and food.

The other exposure factor in the equation, water intake (in L/day), represents the amount of tap water which an individual consumes as drinking water, as well as mixed with beverages and used in cooking. The adult default for this factor is 2 L/day at an assumed body weight of 70 kg. For small children, 1 L/day is used, based on a 10 kg body weight. For 2,4-D, dermal absorption and other incidental exposures to the chemical in drinking water should not contribute significantly to the total dose because 2,4-D does not penetrate skin well, and is not volatile enough to provide a secondary inhalation exposure from other household water uses. Therefore the total equivalent water exposure (Leq/day) will be considered to be that obtained from drinking the standard volume of water (2 L/day).

Therefore,

\[
C = \frac{1 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{100 \times 2 \text{ L/day}} = 0.07 \text{ mg/L} = 70 \text{ ppb.}
\]

OEHHA calculates a PHG of 0.07 mg/L (70 ppb) for 2,4-D in drinking water.

**RISK CHARACTERIZATION**

Epidemiological data indicate a potential for tumorigenic and developmental effects of phenoxy herbicides, but the association of increased tumor rates or birth defects with 2,4-D has been weak and inconsistent. The reported adverse effect rates in epidemiological studies have not, in general, been corrected for other risk factors. For example, in the Minnesota birth defect study of Garry et al. (1996), there are many other conditions which differ among the agricultural and urban regions of the state, such as other agricultural related exposures or activities. The various data on increased tumor rates may also reflect earlier exposures to dioxin, a contaminant of phenoxy herbicides, especially 2,4,5-T. Because these data cannot be used for risk assessment, the animal data are used to derive the PHG.
An uncertainty factor of 100 has been incorporated into the PHG to help protect humans, including sensitive populations, from any adverse effects. The total exposure from food containing trace levels of 2,4-D plus the exposure from drinking water which meets the 2,4-D PHG will be much lower than the doses to workers who have occupational exposures to 2,4-D (HSDB, 1996). The World Health Organization estimated that average daily doses of 2,4-D to the general population are about 0.3 to 2 μg/kg from air, food and water combined (WHO, 1984).

No especially sensitive populations were identified. There is no reason to presume extra sensitivity for infants and children, who should be adequately protected from 2,4-D in drinking water with a 100-fold safety factor plus assuming only 20% of total exposure from drinking water. No synergistic interactions with other chemicals are expected. Intermittent exposures to other phenoxy herbicides are expected from dietary and occupational sources, but concurrent exposures to significant levels of two or more phenoxy herbicides should be rare. Thus, no extra margin of safety to allow for concurrent exposures is considered necessary.
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