

**Public Health Goal for
PICLORAM
in Drinking Water**

Prepared by

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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.

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SUMMARY

A Public Health Goal (PHG) of 500 ppb is developed for picloram in drinking water. The U.S. Environmental Protection Agency's (U.S. EPA's) Maximum Contaminant Level (MCL) for picloram is 500 ppb. This is based on a no-observed-adverse-effect-level (NOAEL) of 7 mg/kg-day from a six month dog feeding study in which the critical health endpoint was increased liver weights. There is no new scientific information that would justify a change in the toxicological endpoint of concern, or the assumptions and uncertainty factors used in the calculation of the PHG. Therefore, the Office of Environmental Health Hazard Assessment (OEHHA) calculates a PHG of 0.5 mg/L (500 ppb) which is expected to be sufficiently health-protective to prevent adverse effects in the general population and in potential sensitive subpopulations based on the data currently available for this chemical.

INTRODUCTION

Picloram (4-amino-3,5,6-trichloropicolinic acid) is a polychlorinated aromatic hydrocarbon widely used as a broad spectrum herbicide for the control of broad-leaved weeds and woody plants along rights-of-way. It is used alone or in combination with 2,4-dichlorophenoxyacetic acid (2,4-D) against deep-rooted perennials on non-crop land and in combination with 2,4-D or 2,4,5-T for brush control (Worthing and Walker, 1987).

The published scientific literature was searched, and relevant articles were obtained on the toxicology of picloram¹. In general, a review of the new scientific literature for picloram did not identify any new studies that would be more appropriate for deriving a PHG for picloram than the studies used previously to derive the state MCL, and U.S. EPA's MCL and Maximum Contaminant Level Goal (MCLG). The federal MCL and MCLG as well as the California MCL and OEHHA's PHG have the same value of 0.5 mg/L (500 ppb).

TOXICOLOGY

Acute Toxicity

Picloram has relatively low acute toxicity in experimental animals (Gorzinski *et al.*, 1987). The acute oral LD₅₀ in rats is approximately 8,200 mg/kg and the dermal LD₅₀ in rabbits is > 4,000 mg/kg (Ben-Dyke *et al.*, 1970). Picloram is readily excreted by rats and humans, primarily unchanged via the urine within six hours of administration (Nolan *et al.*, 1980, 1984; Redemann, 1965; Mullison, 1985).

In a seven-day feeding study, picloram was administered to female dogs (one per dose group) at levels of 400, 800 or 1,600 mg/kg-day (Dow, 1981a). Picloram caused emesis and loss of body weight in female dogs at 800 and 1,600 mg/kg-day. The lowest dose tested, 400 mg/kg-day, was identified as the NOAEL. In another study by Dow (1981b), beagle dogs (one dog per dose) were administered picloram at 200, 400 or 800 mg/kg-day in the diet. Based on reduced food intake at 400 and 800 mg/kg-day, the NOAEL was determined to be 200 mg/kg-day.

¹ A copy of the literature review is available upon request.

Picloram was administered to mice at levels of 0, 90, 270, 580, 900 or 2,700 mg/kg-day in the diet for 32 days (Dow, 1980). Significantly increased liver weights were noted in females at 2,700 mg/kg-day. The NOAEL for this study was 900 mg/kg-day.

Subchronic and Chronic Toxicity

The liver is the primary target for picloram toxicity during chronic as well as subacute and subchronic administration (see reviews by Mullison, 1985; Gorzinski *et al.*, 1987; National Research Council of Canada, 1974). In a 13-week feeding study, Fisher 344 rats (15/sex/dose group) were administered picloram at 0, 15, 50, 150, 300 or 500 mg/kg-day in the diet (Dow, 1983). Liver swelling was observed in both male and female rats at 150 and 300 mg/kg-day. The NOAEL in this study was determined to be 50 mg/kg-day. In another 13-week study conducted in B6C3F1 mice, 10 male and female mice per group were administered picloram in their diet at 0, 1,000, 1,400 or 2,000 mg/kg-day. Liver weights were increased significantly in males and females at all dose levels tested (Dow, 1983).

In a two-year chronic toxicity and oncogenicity study, picloram was administered to Fisher 344 rats (50/sex/dose) in the diet at 0, 20, 60 or 200 mg/kg-day (Stoff *et al.*, 1990). There were no treatment-related increases in the incidence of any particular tumor type or in total tumors. Statistically significant dose-related changes included hepatocellular swelling and altered tinctorial properties in the central regions of the liver lobules and increased relative liver weights in males and females dosed at 60 and 200 mg/kg-day. A NOAEL of 20 mg/kg-day was identified from this study based on histological changes in the liver.

In a six-month feeding study in dogs, picloram was administered at 0, 7, 35 or 175 mg/kg-day in the diet (Dow, 1982). The critical health endpoint was increased liver weights at 35 and 175 mg/kg-day. A NOAEL of 7 mg/kg-day was identified from this study. A two-year oncogenicity bioassay by the National Cancer Institute (NCI, 1978) is discussed below.

Reproductive Toxicity

In the two-year feeding study by NCI (1978) (see above) male Osborne-Mendel rats administered picloram at 370 and 740 mg/kg-day developed testicular atrophy. However, this finding is of questionable toxicological significance since testicular atrophy was also observed in control animals.

McCollister *et al.* (1967) studied reproductive effects of picloram in a three-generation study (two litters per generation). Groups of 4 male and 12 female rats were administered 0, 7.5, 25 or 75 mg/kg-day of Tordon (95% picloram) in the diet. The rats were 11 weeks old at the start of the study and were maintained on the test diets for one month prior to breeding to produce the F_{1a} generation. Litter size was culled to eight pups after five days. Lactation continued until the pups were 21 days old, when they were weaned and weighed. After 7 to 10 days the dam was bred for the F_{1b} generation. The second generation (F_{2a} and F_{2b}) was derived from F_{2b} animals aged 110 days. Two weanlings per sex per dose from litters of each generation were observed for gross pathology. Gross pathology was also assessed on all parent rats and all female non-pregnant rats. Five male and five female weanlings from each group of the F_{3b} litter were selected randomly for gross and microscopic examination of the lung, heart, liver, kidneys, adrenals, pancreas, spleen and gonads. Picloram reduced fertility by 42% in the F_{1b} females of the 150 mg/kg-day dose group,

but this effect was judged as spurious since it was not seen in subsequent generations. No other reproductive effects were noted. The NOAEL in this study was 150 mg/kg-day, the highest dose tested, but the small number of animals examined make this a weak conclusion.

Developmental Toxicity

There is little evidence to suggest that the oral administration of picloram results in teratogenic or other developmental effects in rats, mice or rabbits.

In the McCollister (1967) study described, the F_{1c}, F_{2c} and F_{3c} litters were studied for the teratogenic potential of picloram. The dams were sacrificed on day 19 or 20 of gestation, and offspring were inspected for gross abnormalities, including skeletal and internal structures. Placentas were examined for fetal death or resorptions. No teratogenic effects were observed at any dose level (in a relatively small number of animals, as noted above).

Hayden *et al.* (1963) showed that picloram had no effect on fertility of female mice (strain and number not specified) when compared to an oral contraceptive containing progesterin and estrogen in a ratio of 66:1. Both picloram and contraceptive were administered to fertile mice in the diet at approximate dose levels of 15 mg/kg-day. The female mice receiving the contraceptive became infertile during the treatment period, whereas female mice receiving picloram continued to be fertile during the time of observation.

In a study by Thompson *et al.* (1972) Sprague-Dawley rats were administered picloram on days 6 to 15 of gestation at dose levels of 0, 500, 750 or 1,000 mg/kg-day. Twenty-five females were sacrificed on day 20, and their litters were delivered by cesarean section; 10 additional dams per group were allowed to deliver and wean their pups. Dams receiving 750 or 1,000 mg/kg of picloram developed mild diarrhea and hyperesthesia. There were also 14 maternal deaths between days 8 and 17 of gestation in these groups. In all treatment groups there was an increase in unossified fifth sternbrae, indicative of delayed fetal development. Increased incidences of accessory ribs reflected developmental toxicity at 1,000 mg/kg-day. A LOAEL of 500 mg/kg-day, based on the incidence of unossified sternbrae, was identified in this study.

In another developmental toxicity study, picloram potassium salt was administered to New Zealand rabbits on gestation days 6 through 18 at oral doses of 0, 40, 200 or 400 mg acid equivalent/kg-day (John-Greene *et al.*, 1985). Maternal toxicity (weight loss) was observed during the first three days of treatment at 200 and 400 mg/kg dose levels. There were no signs of developmental toxicity observed in this study. A NOAEL for maternal toxicity of 40 mg/kg-day and a developmental NOAEL of 400 mg/kg-day were identified from this study.

Carcinogenicity

There have been several oncogenicity bioassays of picloram conducted in rats and mice. In an early bioassay (McCollister and Leng, 1969), picloram was administered to groups of male and female Sprague-Dawley rats at dose levels of up to 150 mg/kg-day for two years. No treatment-related effects, including tumorigenesis, were noticed. Further reevaluation of this study revealed, however, several reporting flaws.

A subsequent bioassay was conducted by NCI (1978). In this bioassay, male and female Osborne-Mendel rats were administered picloram at 0, 370 or 740 mg/kg-day for two years in the diet. A treatment-related increase in the incidence of “neoplastic nodules” of the liver was noted in female rats at 370 (10%) and 740 mg/kg-day (14%) compared to controls (0%). It was concluded by the investigators that these data were “suggestive of the ability of picloram to induce benign tumors in the livers of female Osborne-Mendel rats.” The significance of these findings relative to the potential tumorigenicity of picloram was later questioned, however, and picloram was judged to be nontumorigenic in male rats and both male and female mice (NCI, 1978). In addition to the “neoplastic nodules” of liver, increased incidences of thyroid and parathyroid hyperplasia, polyarteritis and testicular atrophy were reported.

Stoff *et al.* (1990) administered picloram at 0, 20, 60 or 200 mg/kg-day for two years in the diet of Fisher 344 rats. No tumor rate increases were observed at the end of the study.

Mutagenicity

Review of the available data indicates that picloram is at most weakly mutagenic. Comprehensive review of picloram’s mutagenic activity is presented by U.S. EPA (1992) in its “Drinking Water Criteria Document.” Review of the more recent literature does not provide any additional supportive or contrary data.

Picloram Herbicide Mixtures

Currently available data indicate that picloram tested alone has very little effect on reproduction and is not teratogenic. However, there are some health concerns related to the use of its mixtures and potential risk for reproductive and developmental effects. The following two reports by Blakley *et al.*, (1989a, 1989b) addressed this issue. The reports described studies on the effects of preconceptional and gestational exposure of CD-1 mice to Tordon 202c. Tordon 202c is a herbicide mixture used in the control of a wide range of annual and deep-rooted perennial broad-leaf weeds. It is composed of picloram (12 g/L) and 2,4-D (200 g/L).

In the first study (Blakley *et al.*, 1989a) pregnant CD-1 mice were exposed to Tordon 202c in the drinking water at concentrations of 0.10, 0.21 or 0.42% from day 6 to 15 of gestation. Fetal growth parameters such as fetal body weight and crown-rump length were reduced in a dose-dependent manner. A dose-dependent decrease in placental weight was also observed. In the highest dosage group there was an increase in dead fetuses, resorptions and malformed fetuses (especially cleft palate). Maternal toxicity in this group was evidenced by decreased water consumption and increased relative liver weight. The authors concluded that Tordon 202c is embryotoxic and teratogenic in CD-1 mice when administered during organogenesis at a dosage that results in slight maternal toxicity.

In the second study Blakley *et al.* (1989b) exposed CD-1 mice to Tordon 202c in the drinking water at concentrations of 0.21, 0.42 or 0.84% for 60 days prior to mating with untreated males. One-half of the pregnant females subsequently continued treatment throughout gestation while the remaining females were maintained on distilled water. Following combined preconceptional and gestational exposure there were reductions in a dose-dependent manner in fetal weight, crown-rump length, placental weight and maternal gestational weight gain. During the same time period, the number of malformed fetuses (cleft palate, renal agenesis, hydronephrosis, unilateral testicular

agenesis and umbilical hernia) and fetuses with variants (especially incomplete ossification of the skeleton) were increased in a dose-dependent manner. In the highest dose group there was increased maternal mortality and decreased preconception weight. The results suggest that the preconceptional and gestational exposure to Tordon 202c is required to cause teratogenesis and fetal growth depression. Preconceptional exposure alone is not effective in increasing the risk for embryotoxicity.

The biological significance of these results in terms of actual human risk is currently unknown. However, due to the persistence of picloram in the environment there is a potential for prolonged exposure to its formulations and such risk should not be overlooked.

DOSE-RESPONSE ASSESSMENT

The California MCL for picloram is currently 0.5 mg/L (500 ppb) (OEHHA, 1993). U.S. EPA's MCL and MCLG for picloram are both 500 ppb. Calculation of these values was based on an NOAEL of 7 mg/kg-day from a six month dog feeding study (Dow, 1982) in which the critical health endpoint was increased liver weights at 35 and 175 mg/kg-day. The MCLG and MCL were calculated from the NOAEL using a 100-fold uncertainty factor, a 20% relative source contribution for drinking water, an adult body weight of 70 kg, and a 2 L/day water consumption.

Review of the currently available data for picloram indicates that there is no other more appropriate study for calculating PHG than the study previously used as a basis for the MCL and MCLG. In this study (Dow, 1982) beagle dogs received daily doses of 0, 7, 35 or 175 mg picloram/kg (six dogs/sex/dose) in the diet for six months. In both male and female groups there were statistically significant ($p < 0.05$) increases in absolute and relative liver weights, decreased body weights and body weight gains, decreased food consumption, and changes in liver enzymes, all observed at the highest dose of 175 mg/kg-day. Statistically significant increases in absolute and relative liver weights were noted as well at the intermediate dose of 35 mg/kg-day in male dogs only. No compound-related effects were detected in female dogs at 35 mg/kg-day and in male or female dogs at 7 mg/kg-day. Based on these results, 7 mg/kg-day was identified as the NOAEL.

OEHHA has therefore chosen 7 mg/kg-day as the NOAEL for calculating a PHG for picloram.

CALCULATION OF PHG

A public health-protective concentration (C) of picloram in drinking water (in mg/L) can be calculated using 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 (7 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 extrapolation and 10-fold for human variability)
L/day = Volume of drinking water consumed daily for an adult (2 L/day).

Therefore,

$$C = \frac{7 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{100 \times 2 \text{ L/day}}$$
$$= 0.490 \text{ mg/L} = 0.5 \text{ mg/L (rounded)} = 500 \text{ ppb.}$$

The PHG for picloram of 0.5 mg/L (500 ppb) is expected to be sufficiently health-protective based on the current data available for this chemical.

RISK CHARACTERIZATION

Major sources of the uncertainties involved in developing the PHG for picloram are related to the default values used in the cumulative uncertainty factor of 100, and the use of a value of 20% for the RSC. The UF of 100 is our default assumption when relying on experimental data from experimentation in laboratory animals and when human data are not available. In this case it should be adequate to provide protection for sensitive subpopulations, including infants and children. The RSC of 20% reflects the assumption that drinking water makes up 20% of the exposure to picloram relative to other sources of exposure. The other 80% comes mainly from the residues of picloram in food which is the most significant source of exposure to this pesticide.

Toxicological data on picloram from laboratory animals are quite extensive. However, data from human studies on carcinogenicity, reproductive and developmental effects, genetic and other related effects are not available. The same applies to mechanistic data which would be needed to understand picloram's toxic actions at the cellular and subcellular level. In addition, because picloram is often used in mixtures with other herbicides such as 2,4-D, more attention should be focused on assessing risk from combined exposure to these chemicals.

REGULATORY STANDARDS AND CRITERIA

The federal MCL and MCLG as well as the California MCL and the OEHHA PHG have the same value of 0.5 mg/L (500 ppb).

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* Proprietary studies