Public Health Goals for
NITRATE AND NITRITE
in Drinking Water

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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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**California Public Health Goal (PHG)**

December 1997

**NITRATE AND NITRITE in Drinking Water**
SUMMARY

OEHHA developed Public Health Goals (PHGs) of 45 ppm for nitrate (equivalent to 10 ppm nitrate-nitrogen), 1 ppm for nitrite-nitrogen and 10 ppm for joint nitrate/nitrite (expressed as nitrogen) in drinking water. The calculation of these PHGs is based on the protection of infants from the occurrence of methemoglobinemia, the principal toxic effect observed in humans exposed to nitrate or nitrite. The PHGs are equivalent to California’s current drinking water standards for nitrate (45 mg/L nitrate), nitrite (1 mg/L nitrite-nitrogen) and 10 mg/L (joint nitrate/nitrite expressed as nitrogen) which were adopted by the California Department of Health Services (DHS) in 1994 from the U.S. Environmental Protection Agency’s (U.S. EPA’s) Maximum Contaminant Levels (MCLs) promulgated in 1991. Following our review of the current literature and a reevaluation of the bases for calculating the MCLs for these compounds, we determined that there was no scientific basis to propose alternative PHGs. Therefore, OEHHA adopts PHGs of 45 mg/L (45 ppm) for nitrate, 1 mg/L (1 ppm) for nitrite-nitrogen and 10 mg/L (10 ppm) for joint nitrate/nitrite (expressed as nitrogen) in drinking water.

INTRODUCTION

California’s current drinking water standard for nitrate is 45 mg nitrate/L (equivalent to 10 mg nitrate-nitrogen/L) and for nitrite is 1 mg nitrite-nitrogen/L. In addition, there is a joint nitrate/nitrite standard of 10 mg/L, expressed on a nitrogen basis. These values were adopted by the DHS in 1994 from U.S. EPA’s MCLs promulgated in 1991. The standards are based on the occurrence of methemoglobinemia, the principal toxic effect observed in humans exposed to nitrate or nitrite. In developing PHGs for nitrate and nitrite, we evaluated the basis for U.S. EPA’s MCLs. In addition, a search of the scientific literature was conducted to determine if there are any new data that would support the development of numbers different from the current values. It is important to note that Office of Environmental Health Hazard Assessment (OEHHA) staff have conducted peer-reviewed, published evaluations of the hazards of nitrate and nitrite in drinking water that were important to the development of PHGs (Fan et al., 1987; Fan and Steinberg, 1996). The results of our present evaluation are described below.

HUMAN EXPOSURE

Human exposure to nitrates and nitrites results primarily from dietary ingestion, particularly from vegetables and cured meats. The average adult daily intake from food in the United States has been estimated to be 40 to 100 mg for nitrate, and 0.3 to 2.6 mg for nitrite. Exposure estimates indicate that for more than 99% of the adult population in the United States, only 1 to 3% of nitrate and nitrite intake comes from drinking water. Drinking water becomes an important contributor to total nitrate exposure only in areas of notable contamination (NRC, 1981; 1995). For infants, the exposure scenarios are somewhat different. For breast-fed infants, total nitrate exposure is negligible. For bottle-fed infants consuming drinking water used to prepare their formula, drinking water can be a substantial exposure pathway. At the MCL of 10 mg nitrate-nitrogen/L, the daily intake for a 4 kg infant consuming 0.64 L/day of water used to prepare formula would be approximately 1.6 mg/kg-day.

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

Methemoglobinemia

Methemoglobinemia is the primary adverse health effect associated with human exposure to nitrate or nitrite. To cause methemoglobinemia, nitrate must be converted to nitrite. Nitrite causes the oxidation of normal hemoglobin to methemoglobin which is unable to transport oxygen from lungs to tissues. Bacteria in the gastrointestinal system mediate the conversion of nitrate to nitrite. Consequently the risk of methemoglobinemia from ingestion of nitrate depends not only on the dose of nitrate by also on the number and type of enteric bacteria. Low levels of methemoglobin occur in individuals with typical values ranging from 0.5 to 2.0% (NRC, 1981). While methemoglobinemia can be clinically diagnosed at levels of 1%, methemoglobin levels up to 10% are generally not considered adverse. At levels above 10%, methemoglobinemia causes cyanosis, and at higher concentrations, asphyxia (WHO, 1996; U.S. EPA, 1997).

Infants are generally recognized as the subpopulation most susceptible to nitrate induced methemoglobinemia (U.S. EPA, 1990; U.S. EPA, 1997). Several factors make infants particularly sensitive to methemoglobinemia including: 1) infants have a greater total fluid intake per unit body weight than adults, 2) the gastrointestinal system in infants normally has a high pH that allows bacterial proliferation and nitrate catalysis to nitrite, 3) frequent occurrences of infant gastroenteritis may favor the development of methemoglobin when the upper gastrointestinal tract becomes colonized with bacteria, 4) fetal hemoglobin is more readily oxidized than adult hemoglobin and 5) infants have half the methemoglobin reductase activity of older children and adults and are therefore less capable of metabolizing excess methemoglobin (Winton et al., 1971; NRC, 1981; Kross et al., 1992).

There are other individuals who may be predisposed to the development of nitrate-induced methemoglobinemia due to altered physiological states. These include pregnant women and possibly others with glucose-6-phosphate dehydrogenase deficiency, adults with reduced gastric acidity (e.g., from diseases including achlorohydria or atrophic gastritis) and those with a lack of methemoglobin reductase (U.S. EPA, 1997; NRC, 1981).

Since the mid 1950’s, more than 2,000 cases of infantile methemoglobinemia have been reported world-wide. Most cases are associated with exposure concentrations greater than 20 mg nitrate-nitrogen/L in drinking water that was used to prepare infant formula. Cases of infantile methemoglobinemia associated with nitrate exposure concentrations of 11 to 20 mg nitrate-nitrogen/L are usually associated with concomitant exposure to water contaminated with bacteria. Thorough reviews of the literature on the occurrence of methemoglobinemia in infants are provided by U.S. EPA (1990), Fan et al. (1987), and Fan and Steinberg (1996).

Only two reports were found documenting cases of infantile methemoglobinemia resulting from ingestion of nitrate-contaminated water since the development of the federal standard in 1991. In Wisconsin, a six-week-old girl was found to have a methemoglobin level of 21.4% after having been hospitalized twice, first for dehydration and vomiting, and later for acute weight loss and limited consumption of formula. Water samples taken during the infant’s hospitalization contained 9.9 and 58 mg nitrate-nitrogen/L as collected from the reverse-osmosis unit and from the well that supplied water to the house, respectively. In addition, an early morning first draw sample collected from the kitchen faucet contained copper levels six-times the federal MCL. The infant’s condition
was attributed to her being given formula mixed with water contaminated with both nitrate and copper (MMWR, 1993). In a recent report from Poland (Lutynski et al., 1996), it was noted that from 1979 to 1992, the Poison Information Center in Krakow documented 239 cases of methemoglobinemia from Krakow and neighboring provinces. Of the 239 cases, 216 involved infants who were fed with nitrate-contaminated well water and carrot soup. Exposure concentrations were not given, and water supplies in the area were characterized as being of very poor quality.

**Reproductive and Developmental Toxicity**

In a recent report by the National Research Council (NRC, 1995), the authors concluded that while data from recent epidemiological studies have suggested an association between maternal nitrate exposure from drinking water and developmental effects in offspring, a definite conclusion on the cause-and-effect relationship cannot be drawn.

Most of the studies in experimental animals have been conducted with nitrite. Data have shown reproductive and developmental toxicity associated with exposure to nitrite, but the effects occurred mostly at very high exposure concentrations which can also produce maternal methemoglobinemia. Teratogenic effects have not been observed in rats, mice, hamsters or rabbits (Fan et al., 1987; Fan and Steinberg, 1996; NRC, 1995).

Since the development of the federal standard in 1991, one report was identified of spontaneous abortions possibly related to consumption of nitrate-contaminated well water in Indiana (MMWR, 1996). Four women living in close proximity reported a total of eight spontaneous abortions from 1991 to 1994. Nitrate concentrations of 19 to 29 mg nitrate-nitrogen/L were measured in well-water sources. Term births occurred before or after the period when each of the four women consumed nitrate-contaminated water. The investigation did not establish a causal link between nitrate exposure from drinking water and spontaneous abortion, but the findings indicate the need for further assessment of the possible effects of nitrate on human reproduction. Developmental effects were reported in rat pups from dams consuming sodium nitrite (2,000 ppm) in drinking water (Nyakas et al., 1994). The observed effects on behavior and adrenal function were attributed to fetal hypoxia caused by severe methemoglobinemia in the pregnant rats.

**Carcinogenicity**

Concern has been raised about a possible increased risk of cancer in humans from the endogenous and exogenous formation of N-nitroso compounds from nitrite, many of which are carcinogenic in animals. However, recent epidemiological studies have not supported an association between nitrate or nitrite exposure from drinking water and increased cancer rates in humans. In experimental animals, nitrate and nitrite have not been shown to be carcinogenic. Nitrite has only been shown to be carcinogenic in animals when administered concurrently with nitrosable amines, apparently as a result of the endogenous formation of carcinogenic amines (WHO, 1996; NRC, 1995; Fan and Steinberg, 1996).

In addition to the cancer studies evaluated by the World Health Organization (WHO, 1996), the National Research Council (NRC, 1995) and U.S. EPA (1991), three recent epidemiological studies were identified examining the effects of nitrate exposure on human cancer risk. The results of one case-control study from Germany (Steindorf et al., 1994) suggest the absence of an association between low nitrate levels in drinking water (16 mg nitrate-nitrogen/L) and the risk of...
brain tumors. Two studies by Morales-Suarez-Varela were published on the impact of elevated nitrate concentrations in drinking water (greater than 50 ppm) on cancer incidence and mortality in Valencia, Spain (Morales-Suarez-Varela et al., 1993; Morales-Suarez-Varela et al., 1995). The authors suggest a possible association between elevated nitrate concentrations in drinking water and cancer of the bladder and stomach. However, a definite cause-and-effect relationship was not shown. Another case-control study conducted in Nebraska examined nitrate in drinking water and the risk of non-Hodgkin’s lymphoma (Ward et al., 1996). Authors reported that long-term exposure to elevated nitrate in drinking water (greater than 50 ppm) may contribute to the risk of non-Hodgkin’s lymphoma, but again, no cause-and-effect relationship was shown.

Other Health Effects

Inorganic and organic nitrite compounds can produce hypotension in humans as a result of direct action on smooth muscle. Therapeutic doses of 30 to 60 mg sodium nitrite are typically used to treat angina pectorus. Organic nitrates can also produce hypotension, although through an indirect mechanism of action, while inorganic nitrate does not produce the effect (U.S. EPA, 1990).

DOSE-RESPONSE ASSESSMENT

The current state and federal MCLs for nitrates and nitrites are based on the occurrence of infantile methemoglobinemia resulting from ingestion of nitrate-contaminated water. The two principal studies used as the basis of these standards are described below.

Bosch et al. (1950) evaluated 139 cases of cyanosis due to methemoglobinemia reported in Minnesota from 1947 to 1949. The 139 cases, which included 14 deaths, occurred in infants under six months of age. Nitrate concentrations were measured in 129 wells used to supply water to the infants with methemoglobinemia. None of the wells contained nitrate concentrations less than 10 mg nitrate-nitrogen/L. Only two of the wells contained 10 to 20 mg nitrate-nitrogen/L, however in both of these cases the diagnosis of methemoglobinemia was considered questionable. Coliform organisms were detected in 45 of 51 samples tested for bacterial contamination.

Walton (1951) reported results of a survey conducted by the American Public Health Association that identified 278 cases of infantile methemoglobinemia associated with consumption of nitrate-contaminated water. Water nitrate concentrations were available for 214 of the 278 cases. Of the 214 cases, none occurred from water nitrate concentrations less than 10 mg nitrate-nitrogen/L, and only five cases (2%) involved infants exposed to 11 to 20 mg nitrate-nitrogen/L. More than 80% of the infants were exposed to nitrate concentrations greater than 50 mg nitrate-nitrogen/L. Data on bacteriological contamination of the water and/or incidence of gastrointestinal disease among the infants were not reported.

Nitrate

Based primarily on the studies of Bosch et al. (1950) and Walton (1951), with support from a large number of additional epidemiological and case studies in humans (including Cornblath and Hartmann, 1948; Simon et al., 1964; Toussaint and Selenka, 1970; Craun et al., 1981; see U.S. EPA, 1990 for descriptions of these and other studies) a no-observed-adverse-effect-level (NOAEL) is identified to be 10 mg nitrate-nitrogen/L. An uncertainty factor of one was applied because the available data provide an adequate NOAEL for the critical toxic effect (methemoglobinemia) in the most sensitive human subpopulation (infants). Therefore, the MCL is
10 mg nitrate-nitrogen/L, or 45 mg nitrate/L (U.S. EPA, 1997), based on early clinical signs of cyanosis associated with methemoglobinemia in infants.

Nitrite

There are no reliable quantitative data on nitrite and methemoglobinemia in humans. While nitrite has been shown to cause methemoglobinemia in animals, humans appear to be more sensitive to nitrite-induced methemoglobin formation. Therefore, the MCL for nitrite was derived by extrapolation of nitrate toxicity data in humans. Based on data which indicate that the fraction of nitrate reduced to nitrite in adults is at least 5%, and knowing that nitrate reduction in infants is significantly greater than in adults (due to the presence of gastrointestinal bacteria), the conversion rate is estimated to be at least 10% in infants (U.S. EPA, 1990).

Using the same NOAEL selected for nitrate of 10 mg nitrate-nitrogen/L (from Bosch et al., 1950; Walton, 1951), an uncertainty factor of one was applied because the NOAEL was of the critical toxic effect (methemoglobinemia) in the most sensitive human subpopulation (infants). In addition, the NOAEL was multiplied by 0.1 to account for the estimated conversion rate of nitrate to nitrite by gastrointestinal tract bacteria in infants, as described above. Therefore, the MCL for nitrite is 1 mg nitrite-nitrogen/L (U.S. EPA, 1990; U.S. EPA, 1997).

Joint Nitrate and Nitrite

U.S. EPA set a joint standard for the sum of the concentration of nitrate and nitrite at 10 mg/L as nitrogen. The combined standard does not replace the individual MCLs for nitrate or nitrite, therefore the maximum contribution from nitrite cannot exceed 1 mg nitrite-nitrogen/L (U.S. EPA, 1991).

CALCULATION OF PHGS

Public health-protective concentrations (C, in mg/L) are calculated using the general formula for noncarcinogenic endpoints:

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

where,

- NOAEL = No-observed-adverse-effect-level (10 mg nitrate-nitrogen/L)
- BW = Body weight (not applicable)
- RSC = Relative source contribution (not applicable)
- UF = Uncertainty factor (one)
- L/day = Volume of daily drinking water consumption (not applicable).

In the case of nitrate and nitrite, the NOAEL is based on human data for nitrate exposure from drinking water in the most sensitive population (infants). Therefore, the uncertainty factor for human variability is one. No other uncertainty factors are applied. For nitrite, the NOAEL is multiplied by 0.1 to account for the estimated conversion rate of nitrate to nitrite by gastrointestinal tract bacteria in infants, as previously described.
OEHHA staff support U.S. EPA’s previous analysis on nitrate and nitrite. The values consider the conversion of nitrate to nitrite, nitrite-induced formation of methemoglobin, and the general absence of methemoglobinemia occurring at nitrate-nitrogen levels below 10 mg/L based on worldwide epidemiological evidence. The values are protective for infants, the most sensitive population. Review of updated information compiled since the development of the MCLs in 1991 support the earlier findings. In addition, no cases of methemoglobinemia occurring at or below the MCL have been identified in the United States. Therefore, OEHHA adopts the following PHGs:

\[
\begin{align*}
\text{nitrate} & = 10 \text{ mg nitrate-nitrogen/L (10 ppm nitrate-nitrogen)} \\
& = 45 \text{ mg nitrate/L (45 ppm nitrate)}, \\
\text{nitrite} & = 1 \text{ mg nitrite-nitrogen/L (1 ppm) and} \\
\text{joint nitrate/nitrite} & = 10 \text{ mg/L (10 ppm), expressed on a nitrogen basis.}
\end{align*}
\]

These PHGs, as well as current federal MCLs for nitrate and nitrite, should be adequately protective against methemoglobinemia in infants, as well as any potential reproductive or developmental effects.

**RISK CHARACTERIZATION**

Although there are an enormous amount of data on the occurrence of methemoglobinemia in infants ingesting nitrate-contaminated water, there are some uncertainties in the database used for the development for the MCL:

1. The concentration of nitrate is not known in all reported cases of methemoglobinemia, and cases of nitrate-induced infantile methemoglobinemia have been reported in other countries at levels below the MCL. While the reports that indicate cases occurring below the MCL are of uncertain quality (largely due to a lack of controls for the presence of confounding factors), there is the possibility that methemoglobinemia resulting from nitrate ingestion could occur at a nitrate level lower than the MCL.

2. It is possible that methemoglobinemia is more likely associated with nitrate plus bacterial contamination of drinking water. Bacterial contamination favors the conversion of nitrate to nitrite as well as the occurrence of diarrhea, which in infants can increase the risk of methemoglobinemia.

3. There could be unidentified differences among the study populations, including nutritional status, that could contribute to differences in the reported findings. Vitamin C can help reduce the risk of methemoglobinemia from nitrate (NRC, 1995) and some populations have a higher vitamin C intake level than others.

4. There are no known requirements for reporting cases of methemoglobinemia.

5. Infant illness or death from nitrate-induced methemoglobinemia may be misdiagnosed, perhaps as sudden-infant-death-syndrome (Johnson and Kross, 1990).

In light of the above, a particular public health concern regarding the methemoglobinemia data is the finding of a lowest-observed-adverse-effect-level (LOAEL) of 11 to 20 mg nitrate-nitrogen/L with no clear delineation of a NOAEL. It is important to note that, in the United States no cases of methemoglobinemia have been reported at a nitrate concentration at or below the MCL.
Animal experimental data have shown reproductive and developmental toxicity associated with high exposure levels to nitrate and nitrite, which are not likely to be encountered in drinking water. The lowest concentrations associated with developmental effects were reported at 1,000 ppm sodium nitrite in water, with a NOAEL at or around 500 ppm (Roth et al., 1987; Roth and Smith, 1988). At an MCL of 45 ppm nitrate, and assuming a 10% conversion of nitrate to nitrite, the amount of nitrate ingestion from two liters of water would be several hundred times less than this NOAEL (Fan and Steinberg, 1996).

U.S. EPA has adopted a joint standard to account for the possibility of the simultaneous occurrence of nitrate and nitrite in drinking water. The equilibrium of nitrate and nitrite in aqueous environments greatly favors nitrate. Nitrite levels can become significant with bacterial contamination and anaerobic conditions (U.S. EPA, 1990); in such cases nitrite levels would be expected to be high, exceeding the nitrite MCL of 1 mg/L. In light of the environmental characteristics of nitrate and nitrite, and in keeping with U.S. EPA, we have concluded that the joint MCL of 10 mg/L (with the contribution from nitrite not exceeding 1 mg nitrite-nitrogen/L) adequate for the protection of public health.
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