

Assessment date

The risk assessment was originally conducted in 1998. The Final Task Force Meeting in 2003 agreed that this risk assessment be brought forward to this edition of the *Guidelines for Drinking-water Quality*.

Principal reference

WHO (2003) *Nickel in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/55).

12.94 Nitrate and nitrite

Nitrate and nitrite are naturally occurring ions that are part of the nitrogen cycle. Nitrate is used mainly in inorganic fertilizers, and sodium nitrite is used as a food preservative, especially in cured meats. The nitrate concentration in groundwater and surface water is normally low but can reach high levels as a result of leaching or runoff from agricultural land or contamination from human or animal wastes as a consequence of the oxidation of ammonia and similar sources. Anaerobic conditions may result in the formation and persistence of nitrite. Chloramination may give rise to the formation of nitrite within the distribution system if the formation of chloramine is not sufficiently controlled. The formation of nitrite is as a consequence of microbial activity and may be intermittent. Nitrification in distribution systems can increase nitrite levels, usually by 0.2–1.5 mg/litre.

Guideline value for nitrate	50 mg/litre to protect against methaemoglobinaemia in bottle-fed infants (short-term exposure)
Guideline value / Provisional guideline value for nitrite	<ul style="list-style-type: none"> ● 3 mg/litre for methaemoglobinaemia in infants (short-term exposure) ● 0.2 mg/litre (provisional) (long-term exposure) <p>The guideline value for chronic effects of nitrite is considered provisional owing to uncertainty surrounding the relevance of the observed adverse health effects for humans and the susceptibility of humans compared with animals. The occurrence of nitrite in distribution as a consequence of chloramine use will be intermittent, and average exposures over time should not exceed the provisional guideline value.</p>
Guideline value for combined nitrate plus nitrite	The sum of the ratios of the concentrations of each to its guideline value should not exceed 1.
Occurrence	In most countries, nitrate levels in drinking-water derived from surface water do not exceed 10 mg/litre, although nitrate levels in well water often exceed 50 mg/litre; nitrite levels are normally lower, less than a few milligrams per litre.

GUIDELINES FOR DRINKING-WATER QUALITY

Basis of guideline derivation	<ul style="list-style-type: none"> ● nitrate (bottle-fed infants): in epidemiological studies, methaemoglobinaemia was not reported in infants in areas where drinking-water consistently contained less than 50 mg of nitrate per litre ● nitrite (bottle-fed infants): nitrite is 10 times more potent than nitrate on a molar basis with respect to methaemoglobin formation ● nitrite (long-term exposure): based on allocation to drinking-water of 10% of JECFA ADI of 0.06 mg/kg of body weight per day, based on nitrite-induced morphological changes in the adrenals, heart and lungs in laboratory animal studies
Limit of detection	0.1 mg/litre (nitrate) and 0.05 mg/litre (nitrite) by liquid chromatography; 0.01–1 mg/litre (nitrate) by spectrometric techniques; 0.005–0.01 mg/litre (nitrite) by a molecular absorption spectrometric method; 22 µg/litre (nitrate) and 35 µg/litre (nitrite) by ion chromatography
Treatment achievability	<ul style="list-style-type: none"> ● nitrate: 5 mg/litre or lower should be achievable using biological denitrification (surface waters) or ion exchange (groundwaters) ● nitrite: 0.1 mg/litre should be achievable using chlorination (to form nitrate)
Additional comments	<ul style="list-style-type: none"> ● Nitrite can occur in distribution at higher concentrations when chloramination is used, but the occurrence is almost invariably sporadic. Methaemoglobinaemia is therefore the most important consideration, and the guideline derived for protection against methaemoglobinaemia would be the most appropriate under these circumstances, allowing for any nitrate that may also be present. ● All water systems that practise chloramination should closely and regularly monitor their systems to verify disinfectant levels, microbiological quality and nitrite levels. If nitrification is detected (e.g., reduced disinfectant residuals and increased nitrite levels), steps should be taken to modify the treatment train or water chemistry in order to maintain a safe water quality. Efficient disinfection must never be compromised. ● Methaemoglobinaemia in infants also appears to be associated with simultaneous exposure to microbial contaminants.

Toxicological review

The primary health concern regarding nitrate and nitrite is the formation of methaemoglobinaemia, so-called “blue-baby syndrome.” Nitrate is reduced to nitrite in the stomach of infants, and nitrite is able to oxidize haemoglobin (Hb) to methaemoglobin (metHb), which is unable to transport oxygen around the body. The reduced oxygen transport becomes clinically manifest when metHb concentrations reach 10% or more of normal Hb concentrations; the condition, called methaemoglobinaemia, causes cyanosis and, at higher concentrations, asphyxia. The normal metHb level in infants under 3 months of age is less than 3%.

The Hb of young infants is more susceptible to metHb formation than that of older children and adults; this is believed to be the result of the large proportion of fetal

Hb, which is more easily oxidized to metHb, still present in the blood of infants. In addition, there is a deficiency in infants of metHb reductase, the enzyme responsible for the reduction of metHb to Hb. The reduction of nitrate to nitrite by gastric bacteria is also higher in infants because of low gastric acidity. The level of nitrate in breast milk is relatively low; when bottle-fed, however, these young infants are at risk because of the potential for exposure to nitrate/nitrite in drinking-water and the relatively high intake of water in relation to body weight. The higher reduction of nitrate to nitrite in young infants is not very well quantified, but it appears that gastrointestinal infections exacerbate the conversion from nitrate to nitrite.

The weight of evidence is strongly against there being an association between nitrite and nitrate exposure in humans and the risk of cancer.

Studies with nitrite in laboratory rats have reported hypertrophy of the adrenal zona glomerulosa. The mechanism of induction of this effect and whether it occurs in other species is unclear. JECFA developed an ADI of 5 mg of potassium nitrite per kg of body weight based on the NOAEL in these studies.

History of guideline development

The 1958 WHO *International Standards for Drinking-water* referred to nitrates, stating that the ingestion of water containing nitrates in excess of 50–100 mg/litre (as nitrate) may give rise to methaemoglobinaemia in infants under 1 year of age. In the 1963 *International Standards*, this value was lowered to 45 mg/litre (as nitrate), which was retained in the 1971 *International Standards*. The 1971 *International Standards* first mentioned concern over the possibility of nitrosamine formation *in vivo*; as nitrosamines are a possible hazard to human health, the 1971 *Standards* stated that it may eventually become necessary to reduce the level of nitrates in water if it is found that this source makes a significant contribution to the hazard to human health arising from nitrosamines. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, a guideline value of 10 mg/litre for nitrate-nitrogen was recommended. It was also recommended that the guideline value for nitrite must be correspondingly lower than that for nitrate, and it was noted that the nitrite-nitrogen level should be considerably lower than 1 mg/litre where drinking-water is correctly treated. The 1993 *Guidelines* concluded that extensive epidemiological data support the current guideline value for nitrate-nitrogen of 10 mg/litre, but stated that this value should be expressed not on the basis of nitrate-nitrogen but on the basis of nitrate itself, which is the chemical entity of concern to health. The guideline value for nitrate is therefore 50 mg/litre. This guideline value for methaemoglobinaemia in infants, an acute effect, was confirmed in the addendum to the *Guidelines*, published in 1998. It was also concluded in the 1993 *Guidelines* that a guideline value for nitrite should be proposed, although no suitable animal studies of methaemoglobinaemia were available. A provisional guideline value for nitrite of 3 mg/litre was therefore proposed by accepting a relative potency for nitrite and nitrate with respect to methaemoglobin formation of 10:1 (on a molar basis). In the addendum to the *Guidelines*, published

in 1998, it was concluded that human data on nitrite reviewed by JECFA supported the current provisional guideline value of 3 mg/litre, based on induction of methaemoglobinaemia in infants. In addition, a guideline value of 0.2 mg/litre for nitrate ion associated with long-term exposure was derived in the addendum to the Guidelines, based on JECFA's ADI derived in 1995. However, because of the uncertainty surrounding the relevance of the observed adverse health effects for humans and the susceptibility of humans compared with animals, this guideline value was considered provisional. Because of the possibility of simultaneous occurrence of nitrite and nitrate in drinking-water, it was recommended in the 1993 and 1998 Guidelines that the sum of the ratios of the concentration of each to its guideline value should not exceed 1.

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Principal reference

WHO (2003) *Nitrate and nitrite in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/56).

12.95 Nitritotriacetic acid (NTA)

Nitritotriacetic acid (NTA) is used primarily in laundry detergents as a replacement for phosphates and in the treatment of boiler water to prevent accumulation of mineral scale.

Guideline value	0.2 mg/litre
Occurrence	Concentrations in drinking-water usually do not exceed a few micrograms per litre, although concentrations as high as 35 µg/litre have been measured.
TDI	10 µg/kg of body weight, based on nephritis and nephrosis in a 2-year study in rats and using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for carcinogenic potential at high doses)
Limit of detection	0.2 µg/litre using GC with a nitrogen-specific detector
Treatment achievability	No data available
Guideline derivation	
• allocation to water	50% of TDI
• weight	60-kg adult
• consumption	2 litres/day