HISTORY OF GUIDELINE DEVELOPMENT

Nitrate and nitrite

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/l (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/l (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/l 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/l 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/l, 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/l. 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/l 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 second edition of the Guidelines, published in 1998, it was concluded that human data on nitrite reviewed by JECFA supported the guideline value of 3 mg/l, based on induction of methaemoglobinaemia in infants, and the guideline value was no longer designated as provisional. In addition, a guideline value of 0.2 mg/l for nitrate ion associated with long-term exposure was derived in the addendum to the second edition of the Guidelines, based on JECFA's ADI. 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. These guideline values were retained in the third edition of the Guidelines, published in 2004, and an expanded summary statement was published in the second addendum to the third edition, published in 2008. In the fourth edition of the Guidelines, published in 2011, the provisional guideline value of 0.2 mg/L for chronic effects of nitrite that was included in the third edition was suspended and was noted to be under review owing to significant uncertainty surrounding the endogenous formation of nitrite and concentrations in human saliva. The guideline values of 50 mg/l as nitrate ion and 3 mg/l as nitrite ion were retained to protect against methaemoglobinaemia in bottle-fed infants following short-term exposure. These guideline values were brought forward to the first addendum to the fourth edition of the Guidelines, published in 2017. It was noted that the guideline values for both nitrate and nitrite are based on short-term effects; however, they are also considered protective for long-term effects.