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Cyanide in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as International Standards for Drinking-Water. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

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GENERAL DESCRIPTION

Almost all of the recent literature on cyanide has resulted from interest in the root crop cassava, which provides a major part of the diet for between 300 and 500 million people living in developing countries in the tropics and subtropics. If not properly prepared, cassava can contain very high levels of cyanide, and outbreaks of disease have been associated with its consumption.

ANALYTICAL METHODS

Cyanide can be determined in water by both titrimetric and photometric techniques, with a detection limit of 2 μg/litre (*1*).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Water

Cyanides are occasionally found in drinking-water, primarily as a consequence of industrial contamination.

Food

A recent study suggests that dietary exposure to cyanide is considerably greater in developing countries than in developed countries. For a group of 73 subjects in Liberia consuming cassava, the mean daily ingestion of cyanide ion was calculated to be 0.61 mg/kg of body weight (*2*). Although insufficient data are available from which to calculate the average daily intake in developed countries, it is very unlikely to be of this magnitude.

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Cyanide ion is readily absorbed by the gastrointestinal tract and is rapidly converted into thiocyanate by the enzyme rhodanese. Oral and subcutaneous doses of cyanide in rats are excreted as thiocyanate, primarily in the urine (*3,4*). Golden hamsters exposed to cyanide by subcutaneous infusion appeared to excrete only a relatively small percentage (10–15%) of the dose as thiocyanate in the urine (*5*), perhaps because rhodanese activity in hamsters is lower than in rats, and hence they are less able to convert cyanide into thiocyanate (*6*).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Short-term exposure

A reduction in feed consumption and body weight gain was noted in a group of six male and two female African rats fed diets containing potassium cyanide at 2500 mg/kg for 84 days. No effects on the pathology of the thyroid, liver, kidney, and spleen or on serum total proteins, albumin, aspartate aminotransferase, and alanine aminotransferase were observed, but serum urea concentration was elevated (*7*).

Addition of potassium cyanide at a concentration of 200 mg/litre to the drinking-water of a group of seven male Sprague-Dawley rats produced a slight elevation in liver weight but had no effect on body weight gain after 21 days. Addition of potassium cyanide to the diet at 200 mg/kg had no effect on either parameter. However, there was evidence that cyanide added to the diet was quickly lost or bound, and hence actual exposure was likely to have been less

than anticipated. This study also demonstrated that cyanide offers some protection against selenium toxicity in rats, possibly through the formation of the SeCN ion (*8*).

Six weanling pigs were fed a diet containing potassium cyanide (500 mg of cyanide per kg) for 56 days. A reduction in feed intake was noted, but there was no effect on body weight gain. There were no effects on the weights of several organs examined except for some evidence of an increase in thyroid weight. Pathological examination of a range of tissues revealed no treatment-related effects (*9*).

Pigs were fed diets of cassava containing 0, 96, or 400 mg of cyanide per kg for 72 days. A lowering of serum thyroxine was noted at both dose levels. There were no effects on serum total protein, albumin, alanine aminotransferase, and aspartate aminotransferase, but serum urea was elevated (*10*).

Erythrocyte glucose-6-phosphate dehydrogenase activity was significantly depressed in miniature swine receiving oral doses of 1.2 mg of cyanide ion per kg of body weight per day from week 0 to week 12, but activity returned to control levels after week 16. At lower doses of 0.4 and 0.7 mg of cyanide ion per kg of body weight per day, enzyme inhibition was initially delayed; by week 20, activity was significantly lower than in controls and the highest dose group (*11*).

The effects of cyanide on behaviour were studied in pigs given oral doses of 0, 0.4, 0.7, or 1.2 mg of cyanide ion per kg of body weight per day for 6 months. Exposure to cyanide was reported to produce increasing ambivalence and slower response times to stimuli with increasing dose. Behaviours demanding high energy tended to be affected more readily than those demanding low energy. An effect on glucose metabolism was suggested as a possible explanation for this finding. A reduction in serum thyroxine and, more notably, triiodithyronine levels was found at all three doses (*12*). However, clear effects were observed only at the highest dose.

A group of 10 male rats was fed a 10% casein diet containing added methionine, vitamin B_{12}, iodine, and potassium cyanide (1500 mg/kg) for nearly 1 year. Compared with a control group not receiving cyanide, depression of body weight gain was observed throughout the study, but there were no deaths or clinical signs of toxicity. Depression of both plasma thyroxine and the thyroxine secretion rate, suggestive of depressed thyroid function, was evident at 4 months but less so after 1 year. At autopsy, the animals were found to have enlarged thyroids, which may have been the mechanism of adaptation. Some differences in the histopathology of the spinal cord, notably the white matter, were also found between controls and cyanide-treated animals (*13*).

Chicks were fed diets containing up to 30% cassava root meal for 28 days. The cassava root meal itself contained 300 mg of total cyanide per kg. No effects on survival, feeding performance, body weight gain, or haematology were noted. The additional inclusion of 3% cassava foliage meal (containing 156 mg of total cyanide per kg and 20 μg of aflatoxin per kg) resulted in depression of body weight gain (*14*).

Reproductive toxicity, embryotoxicity, and teratogenicity

A group of 20 pregnant female rats was fed cassava diets with added potassium cyanide (500 mg/kg) for about 20 days. After parturition, dams and offspring were continued on the diet for the 21-day lactation period. Some pups were also continued on the diet for a further 28 days post-weaning. No effects on gestation, lactation performance, or growth of offspring were seen. However, if offspring from dams not treated with cyanide were exposed during the post-weaning period only, depression of both body weight gain and feed intake as compared with untreated controls was observed (*15*).

Groups of six pregnant pigs were fed diets of cassava with to which cyanide at levels of 0, 250, or 500 mg/kg (as potassium cyanide) was added until parturition, after which sows and offspring returned to a standard diet for a 56-day lactation period. Dietary cyanide had no effect on the numbers or weights of fetuses. A slight elevation of maternal thyroid weight was noted. Pathological changes were also observed in this organ in animals receiving the highest dose level (*16*). This study suggests that effects may occur in the pig at doses an order of magnitude lower than that noted in short-term studies on the rat.

Pregnant golden hamsters were exposed to sodium cyanide (0.126–0.1295 mmol/kg per hour) on days 6–9 of gestation by infusion via subcutaneously implanted osmotic minipumps. High incidences of resorptions and malformations were seen in the offspring, the most common abnormalities observed being neural tube defects (*5*).

EFFECTS ON HUMANS

Cyanide may lower vitamin B_{12} levels and hence exacerbate vitamin B_{12} deficiency. It has also been linked to an increased incidence of goitre (cretinism) in Zaire through effects on iodine uptake by the thyroid. Those with nutritional inadequacy or inborn metabolic errors are particularly vulnerable (*17*). Chronic effects on the thyroid and particularly on the nervous system were observed in some populations as a consequence of the consumption of inadequately processed cassava containing high levels of cyanide. This problem seems to have decreased significantly in the West African populations in which it was widely reported following a change in processing methods and a general improvement in nutritional status.

GUIDELINE VALUE

There are a very limited number of toxicological studies suitable for use in deriving a guideline value. There is, however, some indication in the literature that pigs may be more sensitive than rats. Only one study is available in which a clear effect level was observed, at 1.2 mg/kg of body weight per day, in pigs exposed for 6 months (*12*). The effects observed were on behavioural patterns and serum biochemistry.

Using the LOAEL from this study and applying an uncertainty factor of 100 to reflect inter- and intraspecies variation (no additional factor for a LOAEL was considered necessary because of doubts over the biological significance of the observed changes), a TDI of 12 µg/kg of body weight was calculated.

An allocation of 20% of the TDI to drinking-water is made because exposure to cyanide from other sources is normally small and because exposure from water is only intermittent. This results in a guideline value of 0.07 mg/litre (rounded figure), which is considered to be protective for both acute and long-term exposure.

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