FOOD SAFETY

doi: 10.14252/foodsafetyfscj.2013007

Fluorine

Executive Summary

Food Safety Commission of Japan
December 2012 – FS/1052/2012

The Food Safety Commission of Japan (FSCJ) was asked by the Ministry of Health, Labour and Welfare to assess the risks of chemical substances related to the revision of the standards and criteria for 'beverages.' Since fluorine is one of the substances, the risk assessment on fluorine and fluoride was conducted. The data used in the assessment include those from: acute toxicity tests in mice and rats, subacute toxicity tests in mice, rats, rabbits, dogs and pigs, chronic toxicity and carcinogenicity tests in mice, rats and rabbits, neurotoxicity tests in mice and rats, immunotoxicity tests in mice, rats and rabbits, reproductive and developmental toxicity tests in mice and rats, genotoxicity tests, and epidemiological studies and others. Although fluorine has been considered to be an essential element, clear evidence has not been presented. Moreover, its daily minimum requirement has not been established. Epidemiological studies to examine the carcinogenicity of fluoride in drinking water have been conducted, but failed to provide clear evidence of carcinogenicity in humans. Carcinogenicity has not been clearly shown in laboratory animals, either. Fluoride has been reported to be weakly genotoxic in *in vitro* studies using cultured mammalian cells. It is, however, reported that *in vivo* DNA damage tests have not indicated genotoxicity. Taken together, it was considered that fluorine has no genotoxicity relevant to human health. Hence, it was concluded that it is appropriate to specify a tolerable daily intake (TDI) of fluorine in terms of non-carcinogenic toxicity. Based on an epidemiological study of 5,800 children from 12 to 14 years old in the United States, a concentration of 1.0 ppm at which effect was not observed, was taken as a base. Given that the body weight of a child is 20 kg and the amount of water that a child drinks per day is 1 L, no-observed-adverse-effect-level (NOAEL) was calculated to be 0.05 mg/kg body weight per day. Since this value was that obtained from the study of susceptible population, it was considered that this value could be taken as TDI without applying uncertainty factors. As a conclusion, FSCJ specified the TDI of fluorine to be 0.05 mg/kg body weight per day.

Biological Effects of Fluorine and Fluoride

Fluorine has been considered to be an essential element though clear evidence has not been presented. Moreover, its daily minimum requirement has not been established. Fluoride that dissolves in drinking water at low concentrations is known to have an anticaries effect, while it may cause adverse effects on tooth enamel such as dental fluorosis. In addition, other effects such as skeletal fluorosis and an effect on bone fracture in humans have been reported. In laboratory animals, reproductive and developmental toxicities and effects on the nervous system have been reported. Thus, epidemiological studies on these health effects have been conducted.

This is an English translation of excerpts from the original full report.
The original full report is available in Japanese at http://www.fsc.go.jp/fsciis/evaluationDocument/show/kya20030703211.
Since fluorine usually exists as fluorides, the health effects of the compounds were assessed.
Acknowledgement: The FSCJ wishes to thank the members of the Working Group on Beverages for the preparation of this report. The FSCJ also acknowledges the members of Expert Committee on Chemicals and Contaminants for their effort to provide this scientific output.

1. Carcinogenicity and Genotoxicity

The carcinogenicity of fluoride in drinking water has been studied, but clear evidence of carcinogenicity neither in humans nor in laboratory animals has been provided. IARC classified inorganic fluoride into Group 3 'not classifiable as to its carcinogenicity to humans.' Weak genotoxicity was suggested in chromosomal aberration tests of fluoride on cultured mammalian cells, whereas no genotoxicity was indicated with *in vivo* DNA damage tests. Taken together, FSCJ currently judged that fluorine has no genotoxicity relevant to human health. Hence, FSCJ concluded that it is appropriate to specify a tolerable daily intake (TDI) of fluorine in terms of non-carcinogenic toxicity.

2. Effects on Human Health

Concerning effects of oral exposure to fluoride at low concentrations through drinking water on human health, reproductive and developmental effects and effects on the nervous system, bones, and teeth have been studied.

1) Teratogenic Effects and Reproductive Effects

In terms of teratogenic effects, it has been suggested that there is no clear relationship between fluoride in drinking water and congenital malformation. An epidemiological study was conducted in Mexico, where 160 males utilized drinking water that contains fluorine (3.0 ppm). In this study the subjects were divided into two groups: a high exposure group with occupational exposure (3.4 to 27.4 mg/day, or 0.06 to 0.54 mg/kg body weight per day given the body weight of a person to be 50 kg); a low exposure group without occupational exposure (2 to 13 mg/day). The range of exposure doses partially overlapped between two groups. Difference in semen parameters was not observed, whereas effects on the levels of reproductive hormones were observed in the high exposure group.

2) Effects on Children's IQ

Effects on the Intelligence Quotient (IQ) have been studied in 512 children from 8 to 13 years old in China. It has been found that IQ scores of the children in the area with high concentration of fluoride (2.47 ppm) in drinking water were significantly lower than that of children in the area with low concentration of fluoride (0.36 ppm) in drinking water. BMC (The Benchmark Concentration)$_{10}$ and BMCL (The Benchmark Concentration Lower Confidence Limit)$_{10}$ were reported to be 2.32 ppm and 1.85 ppm, respectively, given the cutoff value of IQ 80 and the benchmark response of 10%.

3) Effects on Bones

The results of epidemiological studies in China on the effects on bones have suggested that the excess risk of adverse effects on bones became apparent with total intake of fluorine over 14 mg/day (0.28 mg/kg body weight per day given the body weight of a person to be 50 kg), and that the risk of effects on bones increased with the intake of fluorine of 6 mg/day (0.12 mg/kg body weight per day given the body weight of a person to be 50 kg).

4) Effects on Teeth

Among many studies on the effects on teeth conducted so far, a large-scale survey carried out in China showed that with drinking water containing 1 mg F/L of fluoride dental fluorosis was detectable in 46% of the population examined. However, the details of the report including the intake of fluoride from food were not clear. On the other hand, the results of epidemiological studies in 5,800 children from 12 to 14 years old in the United States have indicated that the incidence of dental fluorosis showed linear relationship with the concentration of fluoride in drinking water at the range of 2 to 10 ppm, but there was no effect on the incidence at the level from 0.1 to 1.0 ppm.

Derivation of NOAEL and Calculation of TDI

From the study above mentioned, FSCJ took the concentration of 1.0 ppm, at which effect was not observed, as a base. Given that the body weight of a child is 20 kg and the amount of water that a child drinks per day is 1 L, fluorine intake from drinking water is calculated to be 0.05 mg/kg body weight per day in the case of drinking water with 1.0 ppm. Although this value is calculated only from intake through drinking water, FSCJ considered this value to be NOAEL as the value from the point of safety, because intake through other foods is unknown. Therefore, more data are required for the estimation of the fraction of fluorine intake from drinking water to the total intake and on the actual exposure to fluorine. Since this NOAEL was obtained from the studies in the susceptible population, FSCJ considered this value as TDI without applying uncertainty factors.

Hence, FSCJ specified the TDI of fluorine to be 0.05 mg/kg body weight per day.

TDI: 0.05 mg/kg body weight per day (as of fluorine)
Basis for TDI specification: Epidemiological study in children from 12 to 14 years old in the United States
Species: Human
Main exposure route: Intake through drinking water
Observational basis for NOAEL establishment: The appearance of dental fluorosis
NOAEL: 0.05 mg/kg body weight per day

<Estimation of Exposure>

When a person weighing 50kg drinks 2 L per day of tap-water containing 0.8 mg /L fluorine, which is the upper limit of drinking water quality standard, the intake amounts to 0.032 mg/kg body weight per day, which is equivalent to 2/3 TDI of 0.05 mg/kg body weight per day.