This is a provisional English translation of an excerpt from the original full report.

Risk Assessment Report
Selenium in Beverages

Food Safety Commission of Japan (FSCJ)

October 2012

Executive summary

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment on selenium, a chemical substance, relating to the revision of the standards and criteria for beverages.

The data used for the assessment include those from: acute toxicity tests in mice and rats, subacute toxicity tests in mice and rats, chronic toxicity and carcinogenicity tests in mice and rats, reproductive and developmental toxicity tests in mice, rats and rhesus monkeys, genotoxicity tests, and epidemiological studies, among others.

Selenium is an essential element for humans, and is mainly ingested from foods in the form of organic selenomethionine and selenocysteine, but actual intake of selenium in each form is unknown. It is generally accepted that selenium compounds, when ingested orally, are quickly absorbed from the gastrointestinal tract. The bioavailability of selenium depends upon its physical properties and chemical forms. Selenium absorbed into the body of mammals plays important physiological roles, such as antioxidant action, in the form of selenoprotein. Either excessive intake or insufficient intake of selenium is known to affect human health.

Human epidemiological studies have shown that insufficient intake of selenium is related to mitochondria myopathy on the one hand, and excessive intake is related to selenium poisoning such as garlic smell in breath and urine, nail abnormalities, alopecia, low hemoglobin value, and CNS abnormality, on the other hand. Examinations in animals have also shown that excessive oral administration of selenium affected the nervous system and tissues of the kidney and liver.

While significant carcinogenicity of selenium has not been reported so far, different tests *in vitro* suggested some genotoxicity of sodium selenite. In addition, genotoxicity of selenium has been suggested by an *in vivo* chromosomal aberration test with two consecutive administrations, though a single intraperitoneal administration showed

negative results. Thus, genotoxicity of selenium cannot be clearly evaluated at the present moment.

Because of these results, the FSCJ did not conclude presently that selenium is carcinogenic, and considered it appropriate to establish a tolerable daily intake (TDI) of selenium in terms of non-carcinogenicity.

According to a health survey in the United States, inhabitants in a farm area with high levels of selenium showed neither significant effects of selenium on biochemical indicators nor clinical conditions such as nail trouble despite selenium intake as high as 240 μg/day on average. Based on this selenium intake level and given the body weight of the inhabitants to be 60 kg, the "no observed adverse effect level" (NOAEL) of selenium was calculated to be 4.0 μg/kg body weight per day. This value is close to 0.87 μg/kg body weight per day which is the recommended daily intake of selenium for North American adults of both sexes. In addition, this survey, conducted in the United States, indicated that even the maximum intake of selenium (724 μg/day), which is three times higher than the average, had no effect. Based on these findings, the FSCJ decided not to apply an uncertainty factor, and established the TDI of selenium to be 4.0 μg/kg body weight per day

III. Risk Assessment

Selenium is an essential element for humans. Selenium is found in various forms in the environment, however the exposure route to humans is mostly through foods and rarely through water and air.

Humans mainly ingest selenium from foods in the form of organic selenomethionine and selenocysteine, but actual intake of selenium in each form is unknown. It is generally accepted that selenium compounds, when ingested orally, are quickly absorbed from the gastrointestinal tract. The bioavailability of selenium depends upon its physical properties and chemical forms. Selenium absorbed into the mammalian body plays important physiological roles, such as antioxidant action, in the form of selenoprotein. Sodium selenite and selenomethionine have been reported to be absorbed, when ingested orally in humans, by more than 80%, regardless of the dosage. On the other hand, the absorption rate of sodium selenite has been reported to be 30% to 46%, which is lower than that of selenomethionine. Both excessive intake and insufficient intake of selenium, however, are known to affect human health.

Human epidemiological studies have shown that insufficient intake of selenium is related to mitochondria myopathy on the one hand, and excessive intake is related to selenium poisoning such as garlic smell in breath and urine, nail abnormality, alopecia,

low hemoglobin value, and CNS abnormality, on the other hand. Abnormality of nails, alopecia, and effects on the liver have been observed in humans exposed to selenium for a long-term period.

Examinations in animals have also shown that the excessive oral administration of selenium affected the nervous system and tissues of the kidney and liver.

Regarding carcinogenicity, no significant carcinogenicity of selenium has been reported. Although a carcinogenicity test where rats were administered with sodium selenate or selenite in their drinking water has reported a significant increase in the incidence rate of malignant tumors, the test has employed only a single dose, and the details of examined organs and the frequency of each type of tumor are unclear. Despite of classification of selenium by IARC into Group 3 (not classifiable as to its carcinogenicity to humans), any finding to suggest human carcinogenicity of selenium has not been obtained. Therefore, selenium cannot be judged to be carcinogenic at this point, though its carcinogenicity cannot be excluded either.

Data on genotoxicity of selenium are controversial. Different examinations *in vitro* have suggested genotoxicity of sodium selenite. Genotoxicity of sodium selenite has been also suggested by an *in vivo* chromosomal aberration test when administered twice, while it could not be observed with a single intraperitoneal administration. As such, genotoxicity of selenium could not be clearly concluded at this point.

On the basis of these findings, the FSCJ concluded that it was appropriate to establish a tolerable daily intake (TDI) of selenium in terms of non-carcinogenicity. Additionally, the FSCJ conducted a risk assessment using the data on human health, because selenium is one of the essential elements for humans and therefore sufficient data of human epidemiological studies are available.

In a survey conducted on 142 inhabitants in a farm area contaminated with high levels of selenium in the United States, neither significant effect on biochemical indicators nor clinical conditions including nail disease was observed in these inhabitants. It is notable that the intake of selenium of these inhabitants was 724 μg/day at maximum, 68 μg/day at minimum, and 240 μg/day on average. Based on the average intake of selenium and given that the body weight of the inhabitants is 60 kg, the FSCJ established the no observed adverse effect level (NOAEL) of selenium to be 4.0 μg/kg body weight per day.

On the other hand, the minimum daily intake of selenium of five Chinese adults living in a farm area with extremely high level of environmental selenium has been reported. The minimum daily intake of selenium of these five inhabitants, who showed

persistent symptoms of selenium poisoning such as abnormality of nails and alopecia, was 913 μg/day converting from the minimum blood level of selenium, 1,054 μg/day.

A reexamination of these five Chinese in 1992 has demonstrated that they had recovered from the selenium poisoning, showing the average blood level of selenium decreased from 1,346 μg/L to 968 μg/L, which is equivalent to 800 μg/day of dietary selenium intake. Given that the average body weight is 55 kg, the LOAEL and NOAEL obtained from this survey are estimated to be 16.6 and 14.5 μg/kg body weight/day, respectively. However, FSCJ deemed those figures unsuitable for TDI establishment because of the limited number (five individuals) of the study population. On the other hand, the NOAEL, 14.5 μg/kg body weight per day, obtained from this survey in China is close to 12 μg/kg body weight per day, the value calculated from the maximum intake (724 μg/day) obtained in the survey in the United States. Hence, FSCJ considered that the results of the survey in China support the results of the survey in the United States.

The recommended daily intake of selenium has been established to be 0.87 μg/kg body weight per day for North American adults of both sexes, and the NOAEL obtained in the survey in the United States, 4.0 μg/kg body weight per day, is close to this recommended value. In addition, this survey conducted in the United States indicated that even the maximum intake of selenium (724 μg/day), which is three times higher than the average, had no effect on human health. Based on these findings, the FSCJ decided not to apply an uncertainty factor to the NOAEL of 4.0 μg/kg body weight per day, and established the TDI of selenium to be 4.0 μg/kg body weight per day

TDI: 4.0 μg/kg body weight/day (of selenium)	
(Basis for TDI establishment):	Epidemiological study
(Observational basis for NOAEL establishment):	Biochemical indicators and clinical conditions including nail disease
(NOAEL):	4.0 μg/kg body weight/day
(Uncertainty factor):	N/A (selenium is an essential element for humans and even an intake of approximately threefold of the NOAEL, which is the maximum intake of selenium, has no effect)

<Reference>

When a person weighing 50 kg daily drinks 2 L of tap-water containing selenium at the upper limit of drinking water quality standard, 0.01 mg /L, the intake amount is to be 0.4 μg/kg body weight per day. This estimated intake is 1/10 of TDI for selenium, that is, 4.0 μg/kg body weight per day.