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

Risk Assessment Report

Aluminium ammonium sulfate, aluminium potassium sulfate

(Food Additives)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted a risk assessment of aluminium ammonium sulfate (CAS No. 7784-26-1, as aluminium ammonium sulfate dodecahydrate, or CAS No. 7784-25-0 as aluminium ammonium sulfate (anhydride)), and aluminium potassium sulfate (CAS No. 7784-24-9 as aluminium potassium sulfate dodecahydrate, or CAS No. 10043-67-1 as aluminium potassium sulfate (anhydride)), based on results from various studies. Both aluminium ammonium sulfate and aluminium potassium sulfate are additives used in baking powder and food manufacturing agent.

The data used in the assessment include pharmacokinetics, genotoxicity, repeated dose toxicity, carcinogenicity, reproductive and developmental toxicity, and human data of aluminium ammonium sulfate, aluminium potassium sulfate, and other aluminium salts as the test substance.

Aluminium ammonium sulfate and aluminium potassium sulfate as additives are reasonably assumed to dissociate to ions, such as ammonium ion, sulfate ion, potassium ion and aluminium ion, in digestive tract and absorbed as these ions. FSCJ considered it necessary, therefore, to evaluate the pharmacokinetics and toxicity of these constituting ions in the risk assessment of the additives, aluminium ammonium sulfate and aluminium potassium sulfate. Accordingly, FSCJ decided to evaluate comprehensively the safety of the additives, aluminium ammonium sulfat and aluminium potassium sulfate, also taking the findings on pharmacokinetics and toxicity of substances that are composed of ammonium ion, sulfate ion, potassium ion and aluminium ion into the consideration.

1. Ammonium ion, sulfate ion and potassium ion

As for ammonium ion, the risk assessment report (2014) of an additive, ammonium isovalerate, has described that the amount of ammonia produced in human digestive tract through food consumption is 10 mg/day in the duodenum and ca. 3g/day in the colon. The ammonia thus produced in digestive tract is mostly absorbed then enters into the portal circulation. In healthy humans, ammonium ion is promptly converted to urea in the liver and the urea is then excreted in urine.

The amount of ammonia incorporated into the human body through ingestion of “aluminium ammonium sulfate” is considered to be within the range of the variance of the amount of ammonia produced through food consumption, and is also considered to be metabolized in the human body in the same manner as the ammonia produced through food consumption. FSCJ decided, therefore, not to conduct evaluation of pharmacokinetics and toxicity of ammonium ion in this assessment.

Pharmacokinetics and toxicity of sulfate ion and potassium ion have been examined in the risk assessment of additives, potassium sulfate (2013) and zinc sulfate (2015), and the conclusion was that that both ions have no concern relevant

to human health. Since no findings that cause safety concern of these ions are newly obtained after that, FSCJ decided not to conduct evaluation of pharmacokinetics and toxicity of sulfate ion and potassium ion.

Hence, FSCJ concluded that there was no finding which suggests safety concerns with sulfate ion, ammonium ion and potassium ion.

2. Aluminium

While Ministry of Health, Labour and Welfare (MHLW) requested FSCJ to conduct this risk assessment of aluminium ammonium sulfate and aluminium potassium sulfate as additives related to revision of the standards for use of additives, the recent risk assessments of aluminium have been conducted not only as additives but also as contaminants by the international organizations since aluminium is contained even in foods in which additives are not used. Therefore, FSCJ considered intake of aluminium both as additives and as contaminants for the assessment of aluminium as ions.

(1) Pharmacokinetics

FSCJ considered that absorption rate of alminium citrate is relatively higher than the other aluminium salts based on the evaluation of various findings on pharmacokinetics of aluminium compounds. Although most of almiminum absorbed in the body is promptly excreted, alminium distributed in the born and other tissues partially poses a long half-life and a potential to cumulate in the body. FSCJ considered consequently that the effects of long-term intake of aluminium must be taken into account for the toxicity evaluation. In addition, alminium shows a long half-life in some tissues such as born and a relatively long-lasting blood concentration even after a single intake of aluminium solution. FSCJ thus considered based on these facts that the effects of aluminium that are attributed to differences in its pharmacokinetics due to the different sources for the intake and the different rout of oral administration such as gavage administration, administration through drinking water and dietary administration are small.

(2) Toxicity

As for alminium salts including these two additives, aluminium ammonium sulfate,and aluminium potassium sulfate, FSCJ judged that these aluminium compounds have no genotoxicity relevant to human health despite the fact that these aluminium compounds cause DNA damage and chromosomal aberration. FSCJ considered that the cells with the damaged DNA are excluded by apoptosis and the chromosomal aberration is caused through rather indirect genotoxic mechanisms.

FSCJ examined the data on acute toxicity, repeated dose toxicity, reproductive and developmental toxicity, and other toxicities of these aluminium compounds. As a result, FSCJ specified the NOAEL of 30 mg/kg bw/day for aluminium ion based on the suppressed body weight gain and effects on the kidney in male offspring observed in the reproductive developmental toxicity studies in rats by Semple (2010) and Poirier et al. (2011).

While effects on the lipid metabolism are observed in rats in a 13-week dietary toxicity study (Kawasaki et al., 1994) and hyperplasia of mucosal epithelium of urinary bladder is observed in a 90-day dietary toxicity study (Sou

et al., 2014) respectively, FSCJ did not judge these effects to be toxicity because no relevant effect has been observed in the other studies. Although effects on the nervous system were observed in 6-month oral exposure tests in rats through drinking water (Somova & Khan (1996), Somova et al. (1997), and Sethi et al. (2008)), the details of the effects are unknown and it is also unclear if the similar pathological findings shall be obtained in humans. In evaluations of the related findings in humans, moreover, evidences for a causal relationship between exposure to aluminium through foods consumption and neurological disease including Alzheimer's disease is thought to be insufficient. Therefore, FSCJ considered that these neurological findings are not of immediate concern for food safety in humans. Two 120-day oral exposure tests through drinking water in rats, by Sun et al. (2011) and by Wang (2012), showed decrease in hormonal level. FSCJ, however, concludes that the effects are not of food safety concerns since no endocrine toxicity has been found in humans.
FSCJ also concludes that aluminium compounds have no carcinogenicity.

FSCJ evaluated the related findings in humans and considered as follows.
Association of aluminium intake and clinical manifestation has been reported for the effects on the born, neurological disease including Alzheimer's disease and dialysis encephalopathy syndrome (DES). It is to note that DES is attributed to Aluminium intake through non-oral administrations.
FSCJ evaluated effects of aluminium intake on the bone based on the following findings. Effects on the bone due to an inhibition of the absorption of phosphoric acid in the digestive tracts under a high-dose administration of antacids, and the effects of aluminium intake through parenteral nutrition in neonates have been suggested by several research reports. Moreover, there are some reports that exclude an association between aluminium level in the bone and hip fracture risks in the elderly. On the basis of these findings, FSCJ concluded that a causal relationship between dietary intake of aluminium and the effects on the bone is unlikely because of insufficient evidences.
FSCJ evaluated potential association between aluminium intake and neurological diseases including Alzheimer's disease based on the reported findings including the case reports published after the evaluation by Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2011. As the result, FSCJ considered that the results from epidemiological studies are controversial, where some suggest potential association between aluminium intake and Alzheimer's disease while others exclude it. In addition, each of these studied individual effects of aluminium intake through either drinking water, foods or medicinal products without consideration of the intake through other routes. The biological mechanism underlying this issue is also obscure. Based on these, FSCJ concluded that the evidence is insufficient to show a causal relationship between dietary intake of aluminium and neurological diseases including Alzheimer's disease.
Hence, FSCJ concluded that dietary intake of aluminium has no food safety concern based on the human data.

(3) Estimated intake
FSCJ estimated intake of aluminium that originated from foods after amendment of standards for use of aluminium ammonium sulfate and aluminium potassium sulfate as additives, and specified it to be 1.0 mg/kg bw/week for children and 0.57 mg/kg bw/week for entire nation (partially including the data on the adults aged 20 years and over). When the intake of aluminium derived from apparatus and containers / packages made with aluminium and from tap

water is added, FSCJ specified the estimated intake to be 1.2 mg/kg bw/week for children and 0.69 mg/kg bw/week for entire nation.

(4) The risk assessment

FSCJ has recognized the necessity to specify an upper limit for intake of aluminium ion derived from additives and contaminants considering the estimated intake of aluminium that originated from foods after amendment of standards for use of aluminium ammonium sulfate and aluminium potassium sulfate as additives.

Regarding the evaluation index of an upper limit for intake of aluminium, JECFA and EFSA employed Tolerable Weekly Intake (TWI)[1] since both organizations evaluated safety risks of the intake of aluminium derived from both additives and contaminants.

For the risk assessment of aluminium as aluminium ion, FSCJ considered intake of aluminium both as additives and as contaminants, as was mentioned above. Considering the recent global trend and the pharmacokinetics as well, FSCJ adopted a TWI as the evaluation index for the risk assessment of aluminium.

A safety factor of 100 was applied to the NOAEL of 30 mg/kg bw/day (as aluminium) obtained in a developmental toxicity study in rats. Converting the value thus obtained to the aluminium intake per a week, FSCJ established a TWI of 2.1 mg/kg bw/week (as aluminium) for aluminium.

[1] JECFA employs PTWI (provisional tolerable weekly intake) instead of TWI. According to EHC 240, PTWI is an evaluation index used for potentially cumulative contaminants, and the term "provisional" is explained as "The use of the term "provisional" expresses the tentative nature of the evaluation, in view of the paucity of reliable data on the consequences of human exposure at levels approaching those with which JECFA is concerned."