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

Risk Assessment Report

Peracetic Acid Preparation and Its Chemical Components (Peracetic Acid, 1-Hydroxyethylidene-1,1-diphosphonic Acid, Octanoic Acid, Acetic Acid and Hydrogen Peroxide)

(Food Additives)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

The Food Safety Commission of Japan (FSCJ) conducted risk assessments of peracetic acid preparation used as an antimicrobial agent as well as its chemical components, based on results from various studies. These include following food additives: peracetic acid (CAS No. 79-21-0); 1-hydroxyethylidene-1,1-diphosphonic acid (HEDP) (CAS No. 2809-21-4); octanoic acid (CAS No. 124-07-2); acetic acid (CAS No. 64-19-7); and hydrogen peroxide (CAS No. 7722-84-1).

The studies used in the assessment include data on the genotoxicity, acute toxicity, repeated dose toxicity, carcinogenicity, reproductive and developmental toxicity, and human data, of peracetic acid, HEDP, octanoic acid, and hydrogen peroxide as test substances.

Since no pharmacokinetic and toxicity data of the peracetic acid preparation are available and also the peracetic acid preparation is composed of the additives as the mixture, FSCJ evaluated food safety of the peracetic acid preparation based on investigation of the safety of its components: peracetic acid; HEDP; octanoic acid; and hydrogen peroxide.

In addition to these additives, peroctanoic acid was also investigated, because of its formation in the preparation of the peracetic acid preparation.

As for acetic acid, FSCJ had evaluated it as an additive in the assessment of “Calcium acetate and calcium oxide (2013)” published in 2013. No pharmacokinetic and toxicological concerns relevant to human health were identified in that assessment. Since then no additional data on the safety concerns have been available. Furthermore, intake of acetic acid is much higher from total diet than from additives. Therefore, FSCJ considered that further investigation was not needed for acetic acid for this assessment.

1. Peracetic Acid and Peroctanoic Acid

1–1. Peracetic Acid

According to JECFA and FSANZ, peracetic acid is unstable and rapidly decomposed in food into water, oxygen and acetic acid, with a half-life of several minutes.

Peracetic acid is rapidly degraded into acetic acid, hydrogen peroxide and oxygen during the heating or in the presence of metal ions. Peracetic acid taken as additives thus reaches the blood circulation with minimal amount. Decomposition seems to occur on the food surface in a manner similar to the chemical and enzymatic degradation. Even if peracetic acid remained on food surface and is ingested by human, it will be decomposed intraorally, nonenzymatically in the digestive tract, or intracellularly, in spite of the stability in the stomach with a low pH.

Peracetic acid has no genotoxicity relevant to human health.

In studies on acute toxicity, repeated dose toxicity and reproductive and developmental toxicity, no irritative effect was observed on peracetic acid to the gastric mucosa, and no apparent toxicity was observed in a 13-week gavage administration study in rats of peracetic acid at the doses below 0.25 mg/kg bw/day (as peracetic acid). Moreover, FSCJ did not find any evidence on which carcinogenicity of peracetic acid could be judged.

The estimated daily intake (EDI) of 0.105 mg/person/day (0.0019 mg/kg bw/day) has been proposed by the applicant for total peroxides including peracetic acid, peroctanoic acid and hydrogen peroxide as an additive preparation in Japan. The value was estimated based on the detection limits of total peroxides in EU residue studies, without considering cooking processes for meat and poultry meat products as well as some vegetables and fruits. Taking into account stability of peroxides during processing and other factors, FSCJ recognized the actual intake of total peroxides is assumed to be much lower than the above-mentioned EDI.

Based on these facts, FSCJ considers that peracetic acid is of no concern for food safety as long as used appropriately as a food additive, and therefore, it is not necessary to specify ADI[1].

1–2. Peroctanoic Acid

Toxicity of peroctanoic acid was assessed by FDA (2000) as the toxicity of peracid in the comprehensive assessment of peracetic acid and peroctanoic acid. Accordingly, FSCJ considers it possible to evaluate

[1] Hydrogen peroxide, another decomposition product of peracetic acid, is discussed later in the section 4.

food safety of peracetic acid and peroctanoic acid as the combined in an assessment using results from various studies on peracetic acid as the test substance. In the definition of a peracetic acid preparation as an additive preparation, peroctanoic acid is formed from octanoic acid. According to JECFA (2006), the actual concentrations of peracetic acid and peroctanoic acid are 213-220 ppm and 14-25 ppm, respectively, in the peracetic acid preparation in use. This difference of ten-fold suggests that the actual intake of peroctanoic acid is much lower than that of peracetic acid, and therefore FSCJ considers that use of peracetic acid preparation as an additive is of no concern relevant to food safety of peroctanoic acid as long as used appropriately.

2. HEDP

From data on the pharmacokinetics, HEDP showed a low oral bioavailability and is distributed mainly in bone, and then excreted in urine and feces.

HEDP has no genotoxicity relevant to human health.

The no-observed-adverse-effect level (NOAEL) for HEDP is specified as 1.3 mg/kg bw/day based on a 52-week dietary toxicity study in dogs, among the results on acute toxicity, repeated dose toxicity, reproductive and developmental toxicity and allergenicity of HEDP.

There is no concern for carcinogenicity of HEDP.

HEDP·2Na is currently used as clinical purpose and data on adverse effects are available from the clinical use at the dose of 200-1,000 mg/person/day. FSCJ judged, considering these data, that a small amount of HEDP intake as an additive raises no concern for food safety.

In considering the EDI (0.0014 mg/kg bw/day) for HEDP as an additive in Japan, FSCJ specified the ADI of 0.013 mg/kg bw for HEDP, applying a safety factor of 100 to the NOAEL of 1.3 mg/kg bw/day obtained in a 52-week dietary toxicity study in dogs.

3. Octanoic Acid

Octanoic acid injested is nearly completely absorbed as free fatty acid. This acid is partly metabolized and distributed in the body including the adipose tissue.

No genotoxic concern relevant to human health is recognized with octanoic acid.

Human experimental data is available on the injestion of triacylglycerol composed of octanoic acid (trioctanoin). FSCJ recognized that the additive use of octanoic acid has no concern for food safety based

on human data, although transient nausea and abdominal bloating are observed in the experiment of trioctanoin.

No reliable data are available among studies on the acute toxicity, repeated dose toxicity and reproductive and developmental toxicity using octanoic acid as a test substance and thus NOAELs could not be specified. Instead, NOAEL was specified from the data of triacylglycerol containing octanoic acid by 23.2% using rats. The NOAEL was the highest dose at 13,200 mg/kg bw/day for males and 14,600 mg/kg bw/day for females (as triacylglycerol) obtained in a 91-day a dietary toxicity study in rats. In addition, no data suggesting the carcinogenicity of octanoic acid is available.

FSCJ confirmed the EDI of octanoic acid derived from additives to be 3.11 mg/person/day which is equivalent to 0.056 mg/kg bw/day for Japanese population. Intake of octanoic acid derived as a food ingredient in Japan is estimated to be 123 mg/person/day in average in the applicant's documents.

Use of octanoic acid raises no concern for food safety as long as used appropriately as a food additive, based on the above-mentioned NOAEL (around 15,000 mg/kg bw/day) for triacylglycerol as well as the fact that intake of octanoic acid as a food ingredient is much higher than the EDI as an additive. FSCJ concluded that it is not necessary to specify ADI for octanoic acid.

4. Hydrogen Peroxide

Hydrogen peroxide is unstable and rapidly decomposed in foods into water and oxygen, which has a half-life of several minutes according to JECFA and FSANZ.

Enzymes such as catalases mediate the decomposition of hydrogen peroxide into water and oxygen. Glutathione peroxidase and other peroxidases are also known to mediate decomposition of hydrogen peroxide. Decomposition also occurs during the heating or in the presence of metal ions.

Decomposition seems to occur on the food surface in a manner similar to the chemical and enzymatic degradation. Although species differences and human individual differences including acatalasemia are known for the catalase activities, hydrogen peroxide on the food surface is reasonably considered to disappear prior to entering the body.

Hydrogen peroxide *per se* is genotoxic. Hydrogen peroxide injested is, however, readily decomposed. Therefore, FSCJ concluded that hydrogen peroxide used as a food additive in an appropriate way has no substantial human exposure and thus has no genotoxicity relevant to human health.

FSCJ established the NOAEL of hydrogen peroxide to be 30 mg/kg bw/day from a 100-day gavage administration study in rats among the studies of acute toxicity, repeated dose toxicity and reproductive

and developmental toxicity.

Currently no available data are provided for carcinogenicity of hydrogen peroxide. No carcinogenicity was suggested in an 18-month oral exposure test in rats through drinking water, whereas high incidence of duodenal carcinomas was observed in mice with decreased catalase activity after hydrogen peroxide exposure. It is not appropriate to extrapolate the mouse carcinogenicity data to human with normal catalase activities. Therefore, FSCJ concluded that hydrogen peroxide has no carcinogenic concern relevant to health in human with normal catalase activities.

The EDI of 0.105 mg/person/day (0.0019 mg/kg bw/day) has been proposed by the applicant for total peroxides including peracetic acid, peroctanoic acid and hydrogen peroxide as an additive preparation in Japan. The value was estimated based on the detection limits of total peroxides in EU residue studies, without considering cooking process for meat and poultry meat products as well as some vegetables and fruits. Taking into account all of the food processing factor, FSCJ recognized the actual intake of total hydrogen peroxide is assumed to be much lower than the above-mentioned EDI.

The standard for use in the current risk control measures prescribes that hydrogen peroxide should be decomposed or removed during manufacturing of the final food products in the risk control measures. As long as the appropriate control measures are implemented, hydrogen peroxide used as an additive is effectively diminished in the final food products.

Consequently, FSCJ concludes that the use of hydrogen peroxide as an additive is of no concern relevant to human health. Although a reliable NOAEL was obtained from various studies, it is unnecessary to specify ADI considering the instability, metabolism and disposition, amounts of actual intake and current control measures of hydrogen peroxide.

As was mentioned above, a high incidence of duodenal carcinomas was observed in mice with decreased catalase activities after the administration of high amounts of hydrogen peroxide. Actual intake of hydrogen peroxide is, however, extremely low in humans. Even if ingested, enzymes other than catalases would mediate decomposition of hydrogen peroxide in saliva and other tissues even in humans with acatalasemia. Therefore, FSCJ concludes that use of hydrogen peroxide as an additive is of no concern relevant to health in humans with both normal and decreased catalase activities as long as it is appropriately used as an additive.

Based on all of the above-mentioned consideration, FSCJ concluded that the use of the peracetic acid preparation and its chemical components raises no concern relevant to human health as long as used appropriately as additives.