Risk Assessment Report

Food Allergens:

Eggs

Food Safety Commission of Japan (FSCJ)
June 2021

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Chronology of Discussion

Self-Tasking risk assessment

29 March	2016	The 600th Meeting of the Food Safety Commission (The Food Safety Commission decided to conduct as Self-Tasking risk assessments)
26 September	2017	The 667th Meeting of the Food Safety Commission (The Food Safety Commission decided to establish the Working Group on Food Allergy)
14 December	2017	The 1st Meeting of the Working Group on Food Allergy (WGFA)
8 March	2018	The 2nd Meeting of the WGFA
13 September	2018	The 3rd Meeting of the WGFA
27 June	2019	The 4th Meeting of the WGFA
19 September	2019	The 5th Meeting of the WGFA
28 November	2019	The 6th Meeting of the WGFA
28 November	2019	The 7th Meeting of the WGFA
5 March	2020	The 8th Meeting of the WGFA
9 July	2020	The 9th Meeting of the WGFA
10 September	2020	The 10th Meeting of the WGFA
29 October	2020	The 11th Meeting of the WGFA
3 December	2020	The 12th Meeting of the WGFA
10 February	2021	The 13th Meeting of the WGFA
17 February	2021	The 14th Meeting of the WGFA
4 March	2021	The 15th Meeting of the WGFA
20 April	2021	The 813th Meeting of the Food Safety Commission (The WGFA reported to the Food Safety Commission that public comments would be opened)
8 June	2021	The 819th Meeting of the Food Safety Commission (Notice to the Consumer Affairs Agency and the Ministry of Health, Labour and Welfare dated the same date)

List of members of the Food Safety Commission of Japan (FSCJ)

Up to 6 January 2017

Hiroshi Satoh, Chairperson of FSCJ
Yasushi Yamazoe, Acting Chairperson
Susumu Kumagai
Midori Yoshida
Katsue Ishii
Itsuko Horiguchi
Masatsune Murata

Up to 30 June 2018

Hiroshi Satoh, Chairperson of FSCJ
Yasushi Yamazoe, Acting Chairperson
Midori Yoshida
Shigeki Yamamoto
Katsue Ishii
Itsuko Horiguchi
Masatsune Murata

From 1 July 2018

Hiroshi Satoh, Chairperson of FSCJ
Shigeki Yamamoto, Acting Chairperson
Toru Kawanishi
Midori Yoshida
Midori Kasai
Itsuko Horiguchi
Mitsuru Yoshida

List of members of the Working Group on Food Allergy (WGFA), FSCJ

Up to 30 September 2019

Eiji Marui, Chairperson	Reiko Adachi	Reiko Teshima
Atsuo Urisu, Acting Chairperson	Takanori Imai	Yoshikazu Nakamura
Michiko Aihara	Motohiro Ebisawa	Tatsuya Moriyama
Rie Akamatsu	Hiromitsu Ogata	
Hiroshi Akiyama	Hirohisa Saitoh	

From 1 October 2019

Eiji Marui, Chairperson	Reiko Adachi	Kumiko Kanatani*[1]
Hirohisa Saitoh, Acting Chairperson	Hiroaki Itoh	Reiko Teshima
Michiko Aihara	Takanori Imai	Yoshikazu Nakamura*[2]
Rie Akamatsu	Motohiro Ebisawa	Tatsuya Moriyama
Hiroshi Akiyama	Hiromitsu Ogata	

*[1]: from1 April 2020
*[2]: up to 31 March 2020

Special Advisers, the WGFA, FSCJ

The 2nd Meeting of the WGFA
Tatsuki Fukuie
MD., PhD., Division of Allergy, Department of Medical Subspecialties, National Center for Child Health and Development

The 7th Meeting of the WGFA
Atsuo Urisu
Visiting Professor, School of Medicine, Fujita Health University

The 8th Meeting of the WGFA
Atsuo Urisu
Visiting professor, School of Medicine, Fujita Health University
Kumiko Kanatani
Researcher, Japan Environment and Children's study Kyoto Regional Center, Graduate School of Medicine Kyoto University

The 9th Meeting of the WGFA
Atsuo Urisu
Visiting Professor, School of Medicine, Fujita Health University
Yoshikazu Nakamura
Professor, Division of Public Health, Center for Community Medicine, Jichi Medical University

The 10th Meeting of the WGFA
Atsuo Urisu
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The 11th Meeting of the WGFA
Atsuo Urisu
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Yoshikazu Nakamura
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The 12th Meeting of the WGFA
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The 13th Meeting of the WGFA
Yoshikazu Nakamura
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The 14th Meeting of the WGFA
Yoshikazu Nakamura
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Summary

Allergen labeling of prepackaged foods started in 2001, before the enactment of the Food Safety Basic Act (Act No. 48, 2003), which established the Food Safety Commission of Japan (FSCJ). Because the FSCJ deemed it necessary to examine Japan's allergen labeling system to ensure the food safety of people with food allergies, the FSCJ conducted a Self-Tasking risk assessment between 2016 and 2021 on allergen labeling of prepackaged foods.

Food allergies can be caused by very small amounts of food allergens and thus prepackaged foods containing allergenic ingredients are, in principle, required to be labeled as containing allergens, regardless of the intention of use as ingredients in Japan's allergen labeling system, which is one of the most important risk management measures for allergens. There are seven specific ingredients that must be declared on prepackaged foods (mandatory labeling) and 21 ingredients that are recommended to be declared[1].

FSCJ selected eggs[2] for its Self-Tasking risk assessment because of the high prevalence of egg allergy among food allergies in Japan and the abundance of scientific findings on egg allergy. Although the scope of “eggs” as a specific ingredient includes edible poultry eggs in general, most of the scientific findings obtained for assessment were related to hen's eggs. Based on the fact that most of the edible poultry eggs consumed by Japanese are hen's eggs, the FSCJ examined mainly the scientific findings related to hen's egg allergy.

Clinically, patients with hen's egg allergy are told by their doctors to check allergen labeling before consuming prepackaged foods. According to previous reports, most patients with food allergies actually check labels when they purchase prepackaged foods. Therefore, it is presumed that patients who are instructed by their doctors to avoid eggs do not consume foods labeled with “eggs” in principle. In fact, clinicians don’t see major problems with the actual allergen labeling system; they haven’t encountered severe cases as far as egg-allergy patients avoid prepackaged foods labeled with “eggs”. In addition, to the extent that a literature search permits, there have been no cases of allergic symptoms induced by hen's egg protein at levels below the “threshold concentration” for labeling purpose in Japan's allergen labeling system, which is 10 micrograms of allergen protein per 1 gram of food.

[1] The incidences of allergic symptoms due to these 21 ingredients are low compared with those due to seven specific ingredients and the severity of allergic symptoms due to these 21 ingredients is reported to be milder than that due to seven specific ingredients in a nationwide prospective survey conducted every three years with the cooperation of about 1,000 clinicians specialized in allergies.

[2] Hereinafter, eggs as a specific ingredient is referred to as “eggs”.

As for the labeling of “eggs” on prepackaged foods, previously published inspection reports by local authorities suggest that concentrations of the “eggs” protein in prepackaged foods without “eggs” labeling are kept at low levels[3]. Meanwhile, some reports of manufactures’ voluntary recall cases per year due to inappropriate labeling are reported, though the number of instructions or orders based on the Food Labeling Act (Act No. 70 of 2013) is small. Reasons for these voluntary recall cases include revealing of the use of “eggs” as ingredients in products without “eggs” labeling and mislabeling of the products.

Generally, in Japan's food industry, allergen management to reduce risks is ensured by good hygiene practices and standard operational procedures. The prevention of unintended presence of allergens in prepackaged foods is generally realized by good hygiene practices such as minimizing the likelihood of allergen cross-contact, and appropriate cleaning and washing in the facilities. Planning and implementation of standard operational procedures in the process of printing and applying labels are also important to ensure appropriate labeling. With the introduction of mandatory HACCP (Hazard Analysis and Critical Control Point)-based approach in the Japan’s food industry, it is expected that appropriate control measures, including prevention of allergen cross-contact as well as labeling errors, will be well implemented, and consequently quality control and quality assurance for appropriate allergen labeling will be further enhanced.

The doses of allergen protein inducing allergic symptoms may vary depending on individuals, and, allergic symptoms can be induced by as little as a few micrograms of egg protein for some individuals. Therefore, patients with food allergies, not just those with egg allergies, need to consume prepackaged foods under the guidance of their doctors. Nevertheless, the likelihood of allergic symptoms induced by consumption of prepackaged foods among patients with egg allergies is considered to be very low, thanks to the mandatory allergen labeling system in Japan.

The FSCJ concludes that the current allergen labeling system in Japan is generally appropriate, judging from the evidence available for “eggs”.

For refinement of risk assessment of food allergens, it is important to continuously accumulate scientific evidence such as information on secular trends in the prevalence of food allergies based on nationwide epidemiological surveys and research data on eliciting doses determined by oral food challenges, and so on.

[3] According to inspection reports by local authorities, concentrations of the “eggs” protein were lower than 1 μg/g in 75-100 % of the samples taken from prepackaged foods without “eggs” labeling in the market.

I. Background

1. Background and Terms of Reference

The Food Safety Commission of Japan (FSCJ) is a risk assessment organization for science-based assessment of food safety risks to human health. The FSCJ conducts risk assessment mainly in response to requests from risk management organizations. The FSCJ also carries out risk assessment on its own initiative when it deems it necessary to examine, which is called Self-Tasking risk assessment. Candidates for the FSCJ's Self-Tasking risk assessment are selected by the members of the Planning Expert Committee based on their impacts on public health in Japan. Then, targets for Self-Tasking risk assessments are determined by the members of the FSCJ, taking account of opinions collected through the public comment procedure.

Food allergy is a phenomenon in which adverse reactions are caused through antigen-specific immunological mechanisms after exposure to a given food. Symptoms of food allergies can range from skin and respiratory symptoms to gastrointestinal symptoms by ingesting a causal food. Anaphylaxis -- severe hypersensitivity reaction that may cause a life-threatening risk with systemic symptoms induced at several organs -- can be seen in patients occasionally.

The Basic Act on Allergic Diseases Measures was enforced on December 25, 2015 (Act No.98 of 2014), and it was stipulated in Article 15 that the government shall take measures to improve the allergen labeling system to prevent severe symptoms and reduce allergic symptoms.

Under the act, the FSCJ decided to examine the allergen labeling system to ensure food safety for those with food allergies. At the 600th meeting (29 March 2016), the FSCJ selected food allergens as the target for its Self-Tasking assessment. At the 667th meeting (26 September 2018), the FSCJ decided to establish the Working Group on Food Allergy (WGFA) to initiate examination following a collection of scientific findings through the research grant and contracted survey programs implemented by the FSCJ.

2. Current Regulations on Food Allergies in Japan

To prevent health hazards to consumers allergic to specific foods, the allergen labeling system was established under the Food Sanitation Act (Act No. 233 of 1947) in 2001. Currently, prepackaged foods containing allergenic ingredients are required to be labeled as containing allergens under the

Food Labeling Act (Act No. 70 of 2013). Food Labeling Standards (Cabinet Office Order No. 10 of 2015), which is pursuant to the provision of Article 4,paragraph (1) of the Food Labeling Act, categorized seven ingredients, including shrimp, crab, wheat, buckwheat, egg, dairy products, and peanuts as specific ingredients that must be declared on prepackaged foods (mandatory labeling). Among food ingredients known to cause immediate-type food allergy, these seven ingredients were considered to be of high necessity for labeling in terms of the prevalence and severity based on the nationwide survey of immediate-type food allergies, which was conducted with the cooperation of doctors specialized in allergy in Japan. In addition, 21 ingredients equivalent to the seven specific ingredients are recommended to be declared pursuant to the Notice Regarding “the Food Labeling Standards” (Vice-Commissioner Notice, Consumer Affairs Agency, No. 139 of March 30, 2015). Those 21ingredients include almond, abalone, squid, salmon roe, orange, cashew nut, kiwi fruit, beef, walnut, sesame, salmon, mackerel, soybean, chicken, banana, pork, matsutake mushroom, peach, yam, apple, and gelatin. (Reference 1)

II. Scope of the Risk Assessment

1. Target Hazards

There are seven specific ingredients and 21 ingredients equivalent to the specific ingredients that are subject to allergen labeling, but, among those, both the quantity and quality of scientific findings on each ingredient vary. Therefore, the FSCJ selected eggs for its Self-Tasking risk assessment because of the higher prevalence of egg allergy among food allergies in Japan and the abundance of scientific findings on egg allergy. Under the Food Labeling Act, the range of egg as a specific ingredient is, in principle, defined in the attached list 1 of Appendix titled “Allergen Labeling” of the Notice Regarding “the Food Labeling Standards” (Vice-Commissioner Notice, Consumer Affairs Agency, No. 139 of March 30, 2015). As shown in the attached list 1, the range of egg is designated by Japan Standard Commodity Classification and includes poultry eggs in general; poultry eggs such as chicken eggs, duck eggs, quail eggs, and other poultry eggs, hen's egg prepackaged food, and other poultry egg prepackaged food. In the Question and Answer Guide Regarding “Food Labeling Standards”(Notice, Consumer Affairs Agency, No. 140 of March 30, 2015), the Consumer Affairs Agency states that the reason for the definition of egg is due to the fact that cross-reactivity (A person who is allergic to hen's egg may be allergic to other poultry eggs) has been observed.

Most of the scientific findings on egg allergy obtained for the assessment were those on hen's eggs, and scientific findings on other poultry eggs were found only in terms of cross-reactivity. In addition, hen's eggs account for the majority of edible poultry eggs consumed in Japan. Therefore, the FSCJ

decided to implement risk assessment on eggs based on the obtained scientific findings on hen's egg and the other poultry eggs if needed.

Hereinafter, eggs as a specific ingredient is referred as “eggs”, and in particular poultry eggs are referred as “hen's egg” for instance.

2. Target Population

The target population for this assessment is people who had already developed allergic symptoms to a particular ingredient in consideration of the concept of selecting foods subject to labeling under the Food Labeling Act. In other words, the FSCJ decided to comprehensively evaluate food allergies induced by the ingestion of the target foods in a group of people who had already been sensitized to them at the level of immunoglobulin E (IgE) antibodies.

Symptoms of food allergy mediated by immunological mechanisms in food allergy can be divided into IgE-mediated and Non-IgE-mediated reactions. IgE-mediated reactions are those involving specific IgE antibodies, and most IgE-mediated reactions correspond to immediate reactions that progress from allergen exposure to symptom induction within two hours, but even in IgE-mediated reactions, symptoms may be induced after two hours in exceptional cases. Non-IgE-mediated reactions are those mediated by immunological mechanisms in which specific IgE antibodies are not proven to be involved, but in which sensitized lymphocytes are proven to be involved, which are called cellular reactions, and generally take several hours to several days from allergen exposure to symptom onset. Food allergies are also classified into the following categories in terms of clinical type: neonatal and infantile gastrointestinal allergy, infantile atopic dermatitis associated with food allergy, immediate-type food allergy, and special type (food-dependent exercise-induced anaphylaxis, oral allergy syndrome). Of these, immediate-type food allergies are the most typical type of food allergy, with symptoms mainly due to immediate-type reactions, the mechanism of which is mainly IgE-mediated. (Reference 2, 3)

As for the ingredients subject to labeling, the seven specific ingredients and the 21 ingredients equivalent to the specific ingredients are determined from the perspective of the number of cases and severity of the allergic symptoms, based on the results of the nationwide survey of immediate-type food allergies conducted with the cooperation of doctors specialized in treatment of allergies in Japan (Reference 4). Therefore, the FSCJ decided to implement a risk assessment on IgE-mediated food allergies as a target disease in this assessment.

III. Definition of Terms

Terms in this assessment report are defined as follows.

1. Food Allergy

Food allergy is a phenomenon in which adverse reactions are caused through antigen-specific immunological mechanisms after exposure to a given food. Please note that the target disease in this assessment report is IgE-mediated food allergy.

2. Allergen and Allergenicity

Immunologically, the term allergen indicates an antigen that induces an allergic reaction. It may also refer to a raw material that causes food allergy. Allergen is defined as “the substance that causes a food allergy” in the Food Labeling Act, Article 4, paragraph (1).

Allergenicity is defined as the ability to induce allergy. In this assessment report, allergenicity is defined as antigenicity against IgE-antibody and includes the ability to induce allergic symptoms.

3. Antigen and Antigenicity

Antigen indicates a substance, which is (mainly protein) that induces specific immune response.

Antigenicity indicates the potential to induce specific immune response. In this assessment report, antigenicity is defined as an ability to induce antibody production *in vivo* and to combine specifically with the antibodies.

IV. Risk Assessment

Hen's eggs are not only consumed raw or cooked, but are also used as raw material for confectionery, breads, and dressings such as mayonnaise. They are also widely used in prepackaged foods due to their emulsifying, foaming, coagulating, water retention, and flavoring properties. For example, they are widely used as a binder for noodles, dairy products, prepackaged meat products, and fish paste products. They are important in the production of prepackaged foods.

In contrast, from the viewpoint of preventing the occurrence of health hazards to consumers with food allergies, “eggs” -- including hen's eggs -- must absolutely be labeled, especially in consideration of the number of cases and severity of allergies. Therefore, it is mandatory to label prepackaged foods in containers and packaging as containing “eggs” as specific ingredients.

To conduct risk assessment for the purpose of examining the allergen labeling system, the FSCJ attempted to collect domestic and foreign scientific research papers on food allergies caused by poultry eggs in general, scientific reports issued by foreign agencies. However, most of the scientific findings obtained were related to hen's eggs. As for the scientific findings on eggs, the FSCJ included materials that did not necessarily have sufficient scientific reliability, such as a small number of cases and lack of peer review. This is because scientific papers pertaining to surveys and research on humans in Japan are especially limited. In this assessment, the FSCJ gathered and organized information on the prevalence, natural history, clinical symptoms, allergenicity, and allergen intake of hen's eggs to understand the actual situation of hen's egg allergy in Japan, and then conducted risk assessment on "eggs".

1. Proportion of Causative Foods of Immediate-Type Food Allergy

From the result of the 2017 nationwide survey of immediate-type food allergies, which targeted food allergy patients who visited health facilities for immediate allergic symptoms, hen's eggs were the most common causative foods, accounting for 34.7 % of all foods surveyed.

By age group, hen's egg accounted for the largest share of 55.3% among 0-year-olds, 38.3% among 1-2-year-olds, and 16.4% among 7-17-year-olds. However, in the age group of 3-6 years, hen's eggs (18.9%) were the second most common food after cow's milk (20.6%), and in the age group of 18 years and above, the share of hen's eggs decreased significantly. (Reference 5)

In the four triennial nationwide surveys of immediate-type food allergies conducted between 2005 and 2014, hen's eggs were also the most common causative foods.

In other surveys of infants and toddlers obtained by the FSCJ, hen's eggs were the most common food causing food allergies. In addition, in a survey of food allergies in school lunches for elementary and junior high school students by Imai and Itabashi (2005), dairy products and egg was the most common causative foods, accounting for about 25% of the total students with allergic symptoms. (Reference 6)

Considering these data, hen's eggs are the most common food causing food allergy in infants. However, many infants develop a tolerance to infantile-onset egg allergy. Therefore, it is suggested that the proportion of hen's egg as a causative food of food allergy decreases with age.

2. Prevalence and Natural History

Several surveys have been reported on the prevalence of food allergies in Japan. However, depending on the purpose of the survey, the target population, criteria (parent report, self-report, and doctor's diagnosis), and the survey, questions varied. Some surveys even included a clinical history of food allergies as a survey question to estimate prevalence. In addition, prevalence depends on the target population or criteria, and such differences make it difficult to compare the results of each survey.

Prevalence of hen's egg allergy by age in Japan was summarized as follows based on the obtained data of the surveys on the prevalence of hen's egg allergy. Please note that the maximum and minimum prevalence are listed if there are multiple reports for a given age group. And if there is only one report for the relevant age group, prevalence from that single report is given.

There have been few reports of nationwide surveys of food allergies in infancy, most of which were conducted in nursery schools and kindergartens, or among infants and toddlers who received health checkups in each region where they lived.

According to the Japan Environment and Children's Study (JECS), a large-scale nationwide, multicenter, prospective birth cohort study in Japan, prevalence of caregiver-reported hen's egg allergy in 2020 was 5.3, 4.7, and 3.2% at age 1, 2, and 3 respectively (Reference 7). Other reported prevalence of hen's egg allergy in infancy can be summarized as 5.5% at age 0, 6.1% at age 1, 3.9% at age 2, 2.5% at age 3, 1.7% at age 4, 1.2% at age 5, 0.4% at age 6, and 3.0% at age 0-6, based on the results of a mixed survey of parent reported and doctor diagnosed cases. In another survey conducted in 2002, prevalence was 1.6 % at age 3-6. Based on test results for specific IgE antibody titer, the prevalence was 0.4-3.2% at age 0 and 5.5% at age 1. Based on food elimination cases oriented by parents, the prevalence was 9.2% at age 1. Based on food elimination cases oriented by doctors, the prevalence was 4.1% at age 3, 0.7% at age 3-6, and 0.96% at the age 0-5, each based on different survey results. Based on the doctor's diagnosis, the prevalence ranged from 3.1 to 3.2% at the age 0-5. Although the prevalence of hen's egg allergy at each age varied depending on the survey target population and the criteria, the prevalence was highest at age 1 and tended to decrease with age thereafter.

In fact, with regard to the natural history of hen's egg allergy, a study of 226 egg-allergic children (aged 1-6 years) in Japan reported that 14% (31/225) had achieved tolerance by age 2, 30% (66/226) by age 3, 59% (133/226) by age 5, 66% (150/226) by age 6, and 73% (164/226) at age 6. (Reference 8)

In the school age group, questionnaire-based surveys and surveys on food allergy response in school lunches have been conducted on a nationwide scale. Based on the results of these surveys, the prevalence of hen's egg allergy was 1.3% in first grade and 0.58% in sixth grade, according to the parent reports. The proportion of food elimination, including both doctor's instruction and self-diagnose, was 2.3% in third grade, 1.02% in first and second grade based on doctor's diagnosis, 0.86-1.5% in third and fourth grade, 0.74% in fifth and sixth grade, 0.34% in junior high school, and 0.34% in high school.

Regarding survey on the prevalence in adulthood, a web survey related to Genome-Wide Association Study on adult women using women's health information service was conducted. In this survey, the prevalence of self-reported hen's egg allergy was 2.4 %. An Internet-based survey on food allergies reported a prevalence of 0.5% based on food elimination, including both doctor's instruction and self-diagnose, and 0.2% based on doctor-instructed food elimination. In the Japan Environment and Children's Study (JECS), the positive proportion of egg white-specific IgE sensitization in mothers was1.0 %. (Reference 9, 10, 11)

There have been few nationwide surveys on the prevalence of food allergies, and the target population, survey questions, and criteria differed due to the purpose of the survey, making it difficult to estimate the true prevalence of hen's egg allergy because of differences in survey results. However, based on current scientific findings, it can be said that the prevalence of hen's egg allergy in Japan is 10% or less at most in infants, 0.3-2% in school-aged children, and lower in adults than in children.

3. Clinical Symptoms

In the egg-based oral food challenge tests in Japan, although the clinical symptoms and their proportions differed in each test due to differences in the purpose of the study, the subjects, and the form of egg intake, skin symptoms were induced in about 60-70%, gastrointestinal symptoms in about 40-80%, respiratory symptoms in about 25-40%, and anaphylaxis in 0-16% of the allergic children.

In the 2014 nationwide survey of immediate-type food allergies, 90.7% of cases diagnosed with egg allergy showed skin symptoms, followed by respiratory symptoms in 25.0%, gastrointestinal symptoms in 21.2%, and mucosal symptoms in 19.1%. In 8.4% of the cases, systemic symptoms (shock) were observed. In contrast, skin symptoms were induced in 88.9%, respiratory symptoms in 37.7%, mucosal symptoms in 30.1%, gastrointestinal symptoms in 23.3%, and systemic symptoms (shock) in 10.5% of all food allergic subjects. Compared to the clinical symptoms of the total subjects,

less than half of the patients with egg allergy showed symptoms of dyspnea, oropharyngeal itching, and hypotension. (Reference 12)

Although the tendency of the symptoms induced by oral food challenge tests and the symptoms reported in the survey of food allergic patients who visited the hospital with immediate symptoms were somewhat different, skin and gastrointestinal symptoms were frequently observed.

Additionally, Food-Dependent Exercise-Induced Anaphylaxis (FDEIA), which is known as a special type of food allergy, was reported less frequently in hen's eggs than other allergen foods, suggesting that FDEIA is less likely to occur in hen's eggs.

4. Allergenicity of Hen's Egg

(1) Identified Allergens

Allergenic proteins (allergen components) in hen's eggs have been identified as ovomucoid, ovalbumin, ovotransferrin, and lysozyme in egg white, and serum albumin (α-livetin) and YGP42 in egg yolk. These proteins have been classified by WHO/International Union of Immunological Societies (IUIS) as Gal d 1 to 6 respectively.

In patients with hen's egg allergy, IgE antibodies bound to egg white proteins have been detected, indicating that allergic reactions are triggered by proteins contained in egg white. It has also been reported that egg yolk can induce allergic reactions, but since it is difficult to clearly separate egg white from egg yolk, some reports suggest that most cases of symptoms induced by egg yolk ingestion are due to contaminated egg white. α-livetin, a protein in egg yolk, is a known causative allergen component in bird-egg syndrome.

Children with prolonged hen's egg allergy have been reported to have higher titers of specific IgE antibodies to ovomucoid than children who have acquired tolerance.

(2) Effects of Food Processing on the Allergenicity

The Allergen proteins in hen's egg may undergo aggregation, degradation, and glycation during food processing or cooking, resulting in changes in allergenicity. In particular, the allergenicity of hen's egg may be reduced due to changes in the dimensional structure of proteins caused by heating. Most of the scientific findings obtained for this assessment reported on changes in the lgE binding ability of allergen components due to egg processing *in vitro*. However, the effect of processing on the IgE

antibody binding ability of allergen components does not necessarily predict the allergenicity of prepackaged foods in food allergic patient population.

When egg white was heated at the low temperature used for sterilization (65℃ for 4 minutes), the IgE antibody binding ability of ovomucoid, ovalbumin, ovotransferrin, and lysozyme was comparable to that of raw egg white. Under insufficient heating conditions (boiling for 10 minutes), the IgE antibody binding ability of ovotransferrin and ovalbumin was not affected. However, when egg white was heated strongly (95℃ for 15 minutes, and boiling for 30 minutes), ovalbumin and ovotransferrin coagulated and became insoluble aggregated proteins, and their IgE antibody binding ability decreased.

In addition, ovomucoid is more heat stable than ovalbumin. Depending on the heating conditions in common cooking process such as boiling, steaming, baking, and frying, ovomucoid may not coagulate even when egg white is heated, and its allergenicity may not be reduced compared to that when unheated. Although there has been very limited research on actual hen's egg dishes, a study by Ozawa and Kato (2002) have examined the change in the amount of salt-soluble ovomucoid due to heating using various cooked hen's egg dishes. Hard-boiled eggs, poached eggs (soft-boiled, hard-boiled), deep-fried eggs (over easy, over hard), and custard pudding decreased salt-soluble ovomucoid levels to varying degrees compared to uncooked eggs. However, soft-boiled egg, Japanese pudding, omelets, Japanese omelet, and scrambled egg, did not decrease salt-soluble ovomucoid levels (Ozawa K et al.,2002). Moreover, since ovomucoid does not coagulate under heating conditions and penetrates the yolk side when left unattended, there is a possibility of ingesting the egg white component even when the yolk is removed from a boiled egg and eaten.

Clinically, it has been recognized that the allergenicity of heated hen's egg differs from that of raw and freeze-dried eggs, and that heating reduces the allergenicity.

Some patients with egg allergy are allergic to raw eggs, but can consume cooked eggs. These individuals have lower egg white specific IgE antibody titers than those who have allergic reactions to cooked egg.

In a double-blind placebo-controlled food challenge by Uris et al. (1997) using freeze-dried egg white, egg white heated at 90℃ for 60 minutes, and ovomucoid-depleted heated egg white in children with high levels of IgE antibodies for egg white, 21 of 38 subjects with positive challenge responses to

freeze-dried egg white had negative challenge responses to heated egg white and ovomucoid-depleted heated egg white, indicating a decrease in allergenicity by heating. (Reference 14)
Therefore, although heating hen's egg may reduce its allergenicity, heating does not necessarily suppress allergic reactions induced by hen's egg, because different allergen components will be affected differently from heating.

It was also reported that the antigenicity of ovomucoid and ovalbumin was reduced by heating the mixture of hen's egg and wheat, and no antigenicity remained depending on the heating conditions. Through the food processing, the allergenicity of the allergen components of hen's egg is affected not only by heat but also by the coexisting raw materials. In addition, it has been reported that the combination of enzymatic and heat treatments reduces the detectable amount of water-soluble allergen components, and the combination of multiple treatments can significantly reduce allergenicity. The degree of change also depends on the type of processing and conditions.

(3) Cross-reactivity

As measured by the antibody binding ability, hen's egg white is cross-reactive to varying degrees with turkey, goose, duck, wild duck, and seagull egg white. However, the only clinical report of an allergic reaction induced in a patient allergic to hen's eggs by ingestion of other avian eggs was a patient with anaphylaxis caused by ingestion of quail egg.

5. Current Risk Management in Japan

“Eggs” is designated as a specific ingredient to allergen labeling under the Food Labeling Standards (Cabinet Office Order No.10 of 2015) pursuant to the provision of Article 4, paragraph (1) of the Food Labeling Act. In the current risk management, the “Interim Report of the Allergen Labeling Study Group of the Research Group on the Social Impact of Food Labeling and its Countermeasures and International Comparison” funded by the Ministry of Health, Labour and Welfare in October 2001stated that if more than a few micrograms of protein weight per milliliter of food or a few micrograms of protein per gram of food were contained in a food, labeling of that allergen was necessary. Therefore, the Ministry of Health, Labour and Welfare designated 10 μg protein/g food (the corresponding allergen soluble protein weight/food weight) as the threshold for monitoring of labeling using analytical methods such as ELISAs (Enzyme-Linked ImmunoSorbent Assay).

Please note that precautionary allergen labeling such as “may contain” is prohibited for specific ingredients and those equivalent to the specific ingredients. However, if unintentional cross-contact during the food manufacturing process is unavoidable despite measures taken to prevent it, it is

desirable to place warnings such as “Manufactured in a plant that also processes *names of specific ingredients*” or “Manufactured in a facility that also processes *names of specific ingredients*” near the list of ingredients. (Reference 1, 4)

Based on the Guidelines for the Implementation of Monitoring and Guidance on Food Sanitation (Notification, The Ministry of Health, Labour and Welfare, No. 301 of 2003), each prefectural governor, mayor of a city establishing health centers, or head of a special ward shall establish plans concerning the following fiscal year’s monitoring and guidance to be implemented by said prefecture (hereinafter referred to as "prefectural plans for the monitoring of and guidance on food sanitation"). With regard to information of violation of labeling of food containing allergens, results of monitoring and guidance by each prefecture have been compiled, but there is no system in place for prefectures to report to the national government. Therefore, there is no comprehensive information for Japan as a whole.

Of the instructions and orders related to the labeling of specific ingredients based on the Food Labeling Act since FY2015, there has been one recall order targeting “eggs” due to missing labeling of a specific ingredient. (Reference 15)

According to the results of the implementation of the Tokyo Metropolitan Government’s prefectural plans for the monitoring of and guidance on food sanitation, the number of items pertaining to allergen inspection based on the Food Labeling Act at public health centers in Tokyo and the Tokyo Metropolitan Institute of Public Health was 67,498 and 209,595 in FY2018, and 59,025 and 210,543 in FY 2017, respectively. In addition, public health centers in the Tokyo and Tokyo Metropolitan Institute of Public Health collect and test food product samples from food manufacturers and food service facilities. They collected 48 samples (wheat, milk, and eggs) in FY2018 and 52 samples (wheat, milk, eggs, and buckwheat) in FY2017, of which wheat was detected in two samples in FY2018 and buckwheat was detected in two samples in FY2017. However, there were no positive cases of “eggs”. (Reference 16, 17, 18, 19)

On the Consumer Affairs Agency Recall Information Site, which provides consumers with information on recalled products gathered by respective ministries, agencies, and local governments according to the laws and regulations and by direct report from responsible business entities to the Consumer Affairs Agency, there have been some reports of manufacturers’ voluntary recall cases per year due to undeclared allergen “eggs” as a specific ingredient. Reasons for the manufacturers’

voluntary recalls included the presence of an undeclared allergen “eggs”, and mislabeling of the products. (Reference 20)

Moreover, in the periodical nationwide survey of immediate-type food allergies in Japan, among those who experienced symptoms within 60 minutes after ingesting food and visited a medical institution (total 4,781 cases), 2.6 % (125 cases including 32 cases of hen's eggs allergy) were reported by doctors as accidental ingestion of food allergens due to mislabeling in the 2017 survey. The result was the same level in the three surveys conducted every three years from 2008 to 2014. (Reference 5, 12, 21, 22).

On the other hand, with regard to food allergy, patients’ awareness of the allergen labeling system, according to a questionnaire survey of food allergy patients’ families in 2003, when the allergen labeling system for prepackaged foods was first launched, 99% of patients’ families checked the label when purchasing food, and about half of the families understood the allergen labeling. In a survey conducted in 2008 targeting food allergy patients and their families, 97 % of the patients said they were aware of and found allergy labels useful, and about 80 % of patients’ parents relied on the allergen labeling system, and had a correct understanding of the allergen labeling system based on self-evaluation. (Reference 23, 24)

6. Estimation of Allergen Intake

There was no information found on the hen's egg intake of the hen's-egg-allergic patient population in Japan, which was the target population of this assessment. In addition, there was no comprehensive information on the range of prepackaged foods containing hen's eggs or on the amount of hen's egg protein in prepackaged foods.

Regardless of intentional or unintentional use, foods containing specific ingredients such as “eggs” must be labeled as containing specific ingredients. People allergic to hen's eggs are generally instructed by their doctors to check the allergen labeling before consuming prepackaged foods, and patients who have been instructed by their doctors to completely eliminate hen's eggs are not considered to be consuming prepackaged food with “eggs” labeling.

Based on the fact that food allergy symptoms can be induced in a short period of time, the FSCJ estimated the amount of unintentional intake of hen's egg protein when a hen's-egg-allergic patient

who had been instructed by his doctor to completely eliminate hen's eggs ate a prepackaged food without “eggs” labeling per serving using the following formula.

The amount of unintentional intake of hen's egg protein when a hen's-egg-allergic patient who has been instructed by his doctor to completely eliminate hen's eggs eat a prepackaged food without “eggs” labeling at a time
= The amount of prepackaged food consumed per serving
×The concentration of hen's egg protein in a prepackaged food without “eggs” labeling

In the estimation, the following points were taken into account. (Reference 1, 25, 26)

- Since there was no data on food intake in the hen's-egg-allergic patient population, the FSCJ used the dataset (daily intake of each food category / person) of 4,503 persons (227 of whom were aged 1 - 6 years, conducted 4 seasons × 3 days/season, for a maximum of 12 a day/ person) from the Dietary Reference Intakes for Japanese project commissioned by the Ministry of Health, Labour and Welfare in fiscal 2005-2007 as food intake data. The dataset was based on a survey of the general population, which suggested that it might not accurately reflect consumption patterns in the allergic consumer and over or underestimate the risk, but it assumed that they were the same as those without food allergy except for the food they were eliminating.
- Since the prevalence of hen's egg allergy was high in infants and young children, the FSCJ extracted data for children (1 - 6 years old in this study).
- This dataset summarized the daily intake of each food for each person. However, since food allergy symptoms were induced in a short period of time by a single food intake, it was desirable to use food intake per serving rather than per day. Accordingly, in making the calculations, it was assumed that a single food was consumed once a day and that one type of food was consumed per serving, although some foods might be consumed multiple times a day, and the median of daily intake of each food group (middle classification) was used as the representative value of the intake of prepackaged foods per serving.
- The food groups (middle category) with the largest median intake by food group (middle category) for children (1 - 6 years old in this survey) was “other dairy products” with intake of 300g, and the next largest was “other beverage” with an intake of 200g. Since “other dairy products” was actually the total intake of breast milk and does not fall under the category of prepackaged foods, the FSCJ therefore decided to use 200g of “other beverage” for the estimation. However, it was assumed that “other beverage” includes tea, coffee/cocoa, and other beverages of taste (barley tea (extract), sports drink, cola, cider) some of which do not actually contain hen's eggs.

- As for the concentration of “eggs” protein in prepackaged foods without “eggs” labeling, no scientific findings showing the actual concentration distribution, including unintentional cross-contact. Therefore, the upper limit of the definition of a trace amount was assumed to be 10 protein μg/g food (the corresponding allergen soluble protein weight / food weight) based on the Japanese food allergen labeling threshold for screening of specific ingredients in food.

Based on the above, it was estimated that the amount of unintentional hen's egg protein ingested by a hen's-egg-allergic patient who has been instructed by a doctor to completely eliminate hen's eggs from his diet was 2 mg/ person / time when he consumed prepackaged foods without “eggs” labeling.

In addition, in the report on the inspection results of specific ingredients, conducted by a prefectural government, a city establishing health centers, or a special ward, the concentration was less than 1 μg/g in 75-100 % of the samples measured by ELISA kits of “eggs” in prepackaged foods without ”eggs” labeling. The “eggs” protein concentration of 10 protein μg/g food used in the estimation was based on the worst-case scenario. Therefore, the assumption of “eggs” protein concentration of 10 protein μg/g food used in the estimation may be an overestimate, and the estimation results may also be an overestimate.

7. Estimation of Eliciting Dose

There have been several reports in Japan and overseas on the amount of hen's egg needed to induce allergic symptoms by oral food challenge tests.

In Japan, there is a study by Urisu et al. (2012) on patients with hen's egg allergy with heated hen's eggs to investigate the minimum dose that could induce allergic symptoms. According to the study, a patient with hen's egg allergy whose allergic symptoms were induced by 2 μg of hen's egg protein was reported. Among the available scientific findings, 2 μg of hen's egg protein was the lowest dose that induced allergic symptoms, but it was the first ingestion during the oral food challenge tests. Therefore, it is possible that allergic symptoms were induced at an even lower dose. (Reference 27)

Sakai et al.(2017) conducted oral food challenge tests with boiled hen's egg white in children under 16 years at the general hospitals in which an allergy specialist was in charge and found that in some

cases, a cumulative dose of 0.1g of hen's egg white (equivalent to 10.5 mg of hen's egg protein[4]) induced allergic symptoms. In other cases, allergic symptoms were induced at 54 g of a cumulative dose of hen's egg white (equivalent to 5,670 mg of hen's egg protein[4]), indicating that there are individual differences in the food allergy eliciting dose. (Reference 28)

Although oral food challenge tests are mainly used to determine the safe intake quantity and judge tolerance acquisition, the scale of the test, the subjects of the tests, the amount of hen's egg protein or the weight of hen's egg (the total challenge dose), the administration intervals, the form of challenge food, and hen's egg content in the challenge food differ from test to test. Consequently, it is difficult to generalize the results from oral food challenge tests and to simply compare the obtained values.

In addition, in studies conducted overseas, the minimum eliciting dose in each oral food challenge test with hen's eggs ranged from a few tens of μg to mg.

Hence, it was confirmed that a few micrograms of hen's egg protein can induce allergic symptoms in some patients. However, in cases where it is estimated from the clinical history that the amount of hen's egg protein that induces allergic symptoms is lower than the challenge dose, the oral food challenge test is not applicable for the patients from an ethical point of view. Given the existence of such patients, it may be possible to set the minimum eliciting dose from oral food challenge tests for individual patients, but it is not possible to set the minimum eliciting dose for the hen's-egg-allergic patient population.

In contrast, an attempt has been made to estimate the probability of inducing hen's egg allergic symptoms in the population with the *benchmark dose* (BMD) *approaches*. Overseas, Taylor et al. (2014) applied Log-Normal, Log-Logistic, and the Weibull distribution models to fit the results of 206 hen's-egg-allergic patients who showed allergic symptoms in double-blind, placebo-controlled food challenge tests (including single-blind food challenge test in part) reported in both published and unpublished reports up to 2013. In the study, from the data on the minimum eliciting dose and cumulative percentage of responses of the individuals who showed allergic reactions, ED_{01} and ED_{05} (ED_p: the dose of an allergen at which a proportion [p] of the allergic population would be likely to react) were estimated. The ED_{01} for objective allergic symptoms was 0.2 mg protein for Log-Normal, 0.12 mg for Log-Logistic, and 0.03 mg protein for the Weibull distribution, and the 95 %lower

[4]The hen's egg protein weight was converted based on the protein weight of 10.5g per 100g boiled hen's egg white listed on the Standard Tables of Food Composition in Japan 2020 (8th edition). (reference 29)

confidence interval of the ED_{05} was 0.62, 0.66, and 0.31 mg protein, respectively. Subsequently, Remington et al. (2020) have estimated ED_p through the use of Stacked Model Averaging Method with the data of 431 cases of oral food challenge tests (basically based on the double-blind, placebo-controlled food challenge tests)for patients with hen's egg allergy. This dataset included articles published between 2011 and 2018 and unpublished clinical data. The Stacked Model Averaging Method utilizes parametric survival distributions including the Weibull distribution, Log-Logistic, Log-Normal, Log-Double-Exponential, and Generalized Pareto to yield estimates of the ED_{01}, ED_{05} for hen's egg. In the study, ED_{01} and ED_{05} of hen's egg were estimated to be 0.2 and 2.3 mg protein, respectively. (Reference 30, 31)

In the analysis of Taylor et al. (2014), three dose-distribution models (Log-Normal, Log-Logistic, the Weibull distribution) were used as mathematical models, but ED_p estimated from each model varied greatly. Generally, these three models were used to estimate ED_p. These models have also been used in other research groups to estimate ED_p of hen's egg. However, there is a large difference in the ED values estimated from the three models, and there is a problem of uncertainty factors in model selection. Recently, Remington et al. (2020) have estimated ED through the use of Stacked Model Averaging Method to solve these uncertainty factors. Hence, further validation, including selection of analysis methods, is considered to be necessary.

8. Conclusion and Subjects for Further Studies

(1) Conclusion

Allergen labeling of prepackaged foods started in 2001, before the enactment of the Food Safety Basic Act, which established the FSCJ. Because the FSCJ deemed it necessary to examine Japan’s allergen labeling system, the FSCJ conducted a Self-Tasking risk assessment on allergen labeling of prepackaged foods.

There are seven specific ingredients that must be declared on prepackaged foods (mandatory labeling) and 21 ingredients that are recommended to be declared. The FSCJ selected eggs for its Self-Tasking risk assessment because of the high prevalence of egg allergy among food allergies in Japan and the abundance of scientific findings on egg allergy.

Most of the scientific findings obtained for assessment were related to hen's eggs, although the scope of “eggs” as a specific ingredient includes edible poultry eggs in general. Based on the fact that most of the edible poultry eggs consumed by Japanese are hen's eggs, the FSCJ examined mainly the scientific

findings related to hen's egg allergy. However, after organizing and analyzing the obtained scientific findings, it became clear that sufficient scientific findings were not prepared for the assessment at this stage.

Under these circumstances, the current situation of “eggs” allergy is as follows based on the obtained findings.

- Hen's eggs are the most common causative foods of food allergies in Japan, accounting for about 35% of all foods surveyed in the 2017 nationwide survey of immediate-type food allergies. (IV. 1. Proportion of Causative Foods of Immediate-Type Food Allergy)

- Based on current scientific findings, it can be said that the prevalence of hen's egg allergy in Japan is 10% or less at most in infants, 0.3-2% in school-aged children, and lower in adults than in children. However, there have been few nationwide surveys on the prevalence of food allergies, and the target population, survey questions, and criteria differed due to the purpose of the survey, making it difficult to estimate the true prevalence of hen's egg allergy because of differences in survey results. (IV. 2. Prevalence and Natural History)

- Both egg white and egg yolk contain allergenic proteins (allergen component) that induce allergic reactions, and through the food processing, the allergenicity of the allergen components of hen's egg is affected. (IV. 4. Allergenicity of Hen's Egg)

- It is confirmed that a few micrograms of hen's egg protein can induce allergic symptoms in some patients based on the results from oral food challenge tests conducted in Japan. On the other hand, there are some patients with egg allergy whose allergic reactions were induced only after ingesting more than a few grams of egg protein, indicating that there was a wide distribution of eliciting dose of hen's egg allergy. However, the scale of the oral food challenge tests and targeted population differ from test to test making it difficult to simply compare the obtained values. (IV. 7. Estimation of Eliciting Dose).

- There was no information found on the amount of unintentional intake of “eggs” protein at one serving in the hen's-egg-allergic patient population in Japan as well as comprehensive information on the amount of “eggs” protein in prepackaged foods. The FSCJ estimated the amount of unintentional intake of hen's egg protein when a hen's-egg-allergic patient who has been instructed by his doctor to completely eliminate eggs eat a prepackaged food without “eggs” labeling at one

serving. And the estimated value was 2 mg in the case of a 200g serving (the largest median daily intake by food group for children aged 1 - 6 years) of prepackaged food containing 10 μg/g of "eggs" protein, which is the reference concentration for labeling in the screening test for “eggs” in prepackaged foods. However, as for the labeling of “eggs” on prepackaged foods, previously published inspection reports by local authorities report that the concentration of “eggs” protein in prepackaged foods notes label as “eggs” was less than 1 μg/g in 75 to 100 % of the samples. The “eggs” protein concentration of 10 μg/g used in the estimation was based on the worst case scenario, which may be an overestimate. Therefore, 2 mg, which is an estimation result, may also be an overestimate. (IV. 6. Estimation of Allergy Intake).

Food allergies can be caused by very small amounts of food allergens and thus prepackaged foods containing allergenic ingredients are, in principle, required to be labeled as containing allergens, regardless of the intention of use as ingredients in current Japan's risk management. Clinically, patients with hen's egg allergy are told by their doctors to check allergen labeling before consuming prepackaged foods. According to previous reports, most patients with food allergies actually check labels when they purchase prepackaged foods. Therefore, it is presumed that patients who are instructed by their doctors to avoid eggs do not consume foods labeled with “eggs” in principle. Clinicians don't see major problems with the actual allergen labeling system; they haven't encountered severe cases as far as egg-allergic patients avoid prepackaged foods labeled with “eggs”. In addition, to the extent the literature search permits, there have been no cases of allergic symptoms induced by hen's egg protein at levels below the “threshold concentration” for labeling purposes in Japanese allergen labeling system, which is 10 micrograms of allergen protein per 1 gram of food.

As for the labeling of “eggs” on prepackaged foods, previously published inspection reports by local authorities reports that the concentration of the “eggs” protein in prepackaged foods note label as “eggs” was less than 1μg/g in 75 to 100% of the samples, suggesting that concentrations of the “eggs” protein in prepackaged foods without “eggs” labeling were kept at low levels. Meanwhile, some reports of manufactures’ voluntary recall cases per year due to undeclared allergens are reported, though the number of instructions or orders based on the Food Labeling Act is small. Reasons for these voluntary recall cases include revealing the use of “egg” as ingredients in products without “eggs” labeling and mislabeling of the products.

Generally, in the Japan’s food industry, allergen management to reduce risks is ensured by good hygiene practices and standard operational procedures. The prevention of the unintended presence of allergens in prepackaged foods is generally realized by good hygiene practices such as minimizing the likelihood

of allergen cross-contact, and appropriate cleaning, and washing in the facilities. Planning and implementation of standard operating procedures in the process of printing and applying labels are also important to ensure appropriate labeling. With the introduction of mandatory HACCP (Hazard Analysis and Critical Control Point)-based approach in the Japanese food industry, it is expected that appropriate control measures, including prevention of allergen cross-contact as well as labeling errors, will be well implemented, and consequently, quality control and quality assurance for appropriate allergen labeling will be further enhanced.

The doses of allergen protein inducing allergic symptoms may vary depending on individuals, and, allergic symptoms can be induced by as little as a few micrograms of egg protein for some individuals. Therefore, patients with food allergies, not just those with egg allergies, need to consume prepackaged foods under the guidance of their doctors. Nevertheless, the likelihood of allergic symptoms induced by consumption of prepackaged foods among patients with egg allergies is considered to be very low, thanks to the mandatory allergen labeling system in Japan.

The FSCJ concludes that the current allergen labeling system in Japan is generally appropriate, judging from the evidence available for “eggs”.

(2) Subjects for Further Studies

This risk assessment was conducted based on currently available scientific findings. Although under the Food Labeling Act, the range of “eggs” as a specific ingredient, which is defined by the Food Labeling Standards, includes poultry eggs in general, most of the scientific findings on egg allergy obtained for the assessment were those on hen's eggs. The FSCJ gathered and organized scientific findings on hen's egg allergy to conduct a risk assessment, and found that scientific findings were limited for quantitative risk assessment.

As for epidemiological data such as prevalence and natural history, there have been few nationwide surveys, and the target population, survey questions, and criteria differed due to the purpose of the survey, making it difficult to estimate the prevalence of hen's egg allergy because of differences in survey results. Moreover, most surveys on the prevalence of food allergy in Japan are based on questionnaire surveys, and it cannot be denied that many patients or family members with allergic reactions or diagnoses of food allergies may have responded to the surveys with low response rates.

In estimating the amount of unintentional hen's egg protein ingested by the “eggs” allergic patients who have been instructed by a doctor to completely avoid hen's eggs from his diet, the FSCJ made

some assumptions in the estimation since there was no information found on the “eggs” intake of the egg-allergic patient population in Japan and the amount of “eggs” protein in prepackaged foods without “eggs” labeling. Using the results of the survey of the general population, the median daily intake of food was assumed to be a single intake, and the concentration of “eggs” protein in prepackaged foods without “eggs” labeling was assumed to be 10 μg/g. However, the differences in dietary habits between the general population and the hen's egg-allergic patient population and the validity of replacing the median daily intake with a single intake have not been clarified. Moreover, in light of the reports on the inspection results of specific ingredients, it is possible that the concentration of “eggs” protein in prepackaged foods without “eggs” labeling is much lower than 10 μg/g, since the labeling system in Japan has already become widespread and Japan's food industry has advanced its management systems, and the estimated results may be an overestimate.

In estimating eliciting dose by ingesting “eggs”, the results obtained by toral food challenge tests differ test to test due to the difference of the scale of the test, targeted population and, so on. Consequently, it is difficult to generalize the results obtained from oral food challenge tests or to simply compare the obtained values. In addition, there is a wide range of estimated values, and the results obtained differ greatly depending on the selection of distribution model used for estimation. Recently, there have been reports that the model averaging approach is applied, and there is still uncertainty factors in utilizing the BMD approach for estimating the population thresholds.

Therefore, it is important to continuously accumulate the scientific evidence to a conduct risk assessment, including further refinement. In particular, it is considered necessary to conduct the following research and collection of information.

- Findings on the secular trends in the prevalence of food allergies based on nationwide epidemiological surveys that incorporate realistic and appropriately designed self-reports, including accurate diagnosis by oral food challenge tests.
- Data from a large-scale study on the eliciting dose using a standardized protocol of oral food challenge tests among allergists nationwide.
- Findings on the frequency and amount of food intake in food allergic patient populations.
- Findings on the amount of prepackaged food consumed per serving estimated based on the latest food intake data.
- Actual data on the amount of “eggs” protein in prepackaged foods distributed in Japan, including not only those that contain “eggs” as ingredients but also those that are mixed in unintentionally.

- Comprehensive data on cases of violation and voluntary recalls of the labeling of foods contain allergens.
- Integrated information on the results of government monitoring of the labeling of foods contain allergens.
- Findings on risk assessment methods for food allergy based on international trends.
- Although not necessarily required for the risk assessment, social scientific findings on the changes in food allergic patients' buying behavior, their awareness, and QOL (Quality Of Life) due to the introduction of allergen labeling system to understand the background of food allergies.

<Abbreviations>

ED	Eliciting Dose
ELISA	Enzyme-Linked ImmunoSorbent Assay
HACCP	Hazard Analysis and Critical Control Point
IgE	Immunoglobulin E
QOL	Quality Of Life

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