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REVIEW

NOVEL INSIGHTS INTO PEDIATRIC ALLERGY AND IMMUNOLOGY

Canned tuna tolerance in children with IgE-mediated fish allergy: an allergological and nutritional view

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ABSTRACT

Scientific research, diagnostic tools and clinical experience have shown that children suffering from IgE-mediated fish allergy do not need to follow a strict exclusion diet. In fact, they could tolerate some species of fish, which could be reintroduced in the diet by verifying their tolerance with an oral food challenge in a clinical setting. Consequently, it is possible to look a new insight on diagnosis and management of IgE-mediated fish allergy in children, considering the use of canned tuna in clinical settings. Authors performed a literature search through the Cochrane Library and Medline/PubMed databases. All quantitative and qualitative pediatric studies involving diagnosis and management of IgE-mediated fish allergy and the use of canned tuna in clinical settings were considered. Articles related to allergological and nutritional features of fish, and especially canned tuna, were selected. This research was conducted on May 2020. Canned tuna shows peculiar allergological and nutritional characteristics. Relating to allergy, canning process, characterized by cooking the fish under pressure for a time equal to about 7 hours, can lead a conformational change in parvalbumin, making it less allergenic. In terms of nutrition, canned tuna contains B, D and A vitamins and, above all, omega-3 fatty acids and shows a favourable and significantly sustainable nutritional profile. Lower allergenicity, adequate nutritional value and its rich availability in markets at reasonable costs, could make the use of canned tuna as a solution with an excellent risk/benefit ratio in the field of IgE-mediated fish allergy.

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Fish is the third most frequent allergen, after egg and cow's milk, in the majority of European countries. The prevalence of IgE-mediated fish allergy is 0.2-2.29% of the general population.[1] This prevalence is variable related to geographical areas, type of fish processing and the frequency of exposure to the different fish species.[2] In children, the diagnosis of fish allergy is common before reaching the age of 2 years, and it often coincides with the first introduction of a fish in the diet.[2] Fish species can be divided into two main groups: bone fish and cartilaginous fish.[2]

The most commonly consumed bone fish belong to the orders of *clupeiformes* (herrings and sardines), *salmoniformes* (salmons and trouts),

cypriniformes (carps), *gadiformes* (cods), *siluriformes* (catfishes) and *perciformes* (perches, mackerels and tunas).[2] Less than 0.5% of all known fish species have been analyzed at the molecular level regarding the allergenic profile.[2] The main allergen identified is a protein called "parvalbumin," which regulates the exchange of calcium in muscle cells.[2, 3] Parvalbumin represents the main fish allergen; specifically, 90% of fish allergic patients react to this protein, which is defined "cross-reactive" for these characteristics.[4, 5] Parvalbumin is present in two isoforms: α and β.[2, 3] The majority of fish often contain both types of parvalbumin; however, it has been shown that the β isoform possesses almost all the allergenicity.[2, 3] Furthermore, most fish express two or more different β isoforms of parvalbumin, (*i.e.* β1, β2), which differ in the amino acids sequence.[2, 6, 7] This situation could explain the fact that a patient, suffering from a food allergy to fish, reacts to one isoform more than another.[7] Given this evidence of different parvalbumin isoforms, it were identified four different IgE epitopes heading against the different parvalbumin isoforms: Baltic Cod (Gad c 1), Carp (Cyp c 1), Mackerel (Sco j 1) and Salmon from the Atlantic Ocean (Sal s 1).[2, 6] At the molecular level, the difference between these four parvalbumin allergens is due to the fact that, structurally, they are proteins which share similar secondary and tertiary structures but a different primary structure.[2, 7] In fish, the beta allergenic form is considered to be a cross-reactive pan-allergen.[2] Although most heat-resistant food allergens contain linear epitopes, parvalbumin contains conformational epitopes, stabilized by the interaction of metal-binding domains.[8] This biochemical aspect could explain the fact that, although parvalbumin is contained in 90% of fish, those subjects suffering from IgE food allergy mediated to the fish, have only about 50% probability of being sensitized and, consequently, to show cross-reaction towards another species of fish.[7]

A further explanation for this phenomenon is due to the peculiar characteristics of the parvalbumin protein.[9, 10] It is known that it is a thermostable protein, not degradable by heat or even by the gastric process in the context of digestion.[9, 10] Recent evidences have shown how this protein is not actually present in the same quantity and distribution in some fish species and that the canning of the fish itself could alter the allergenicity of this protein.[11, 12] Regarding the distribution of parvalbumin within fish, it is almost ubiquitous but, being known that it regulates the exchange of calcium in muscle cells, it is more present at that level.[13] Moreover, it is known that fish is made up of white muscle and red muscle.[13] Parvalbumin is basically contained in the white muscle of the fish. Studies carried out on different species of fish, such as tuna and swordfish, which contains a greater proportion of red muscle, have shown the presence of a low amount of parvalbumin compared to the white muscle.[13] In addition, animal studies have shown that the distribution of parvalbumin is also different within the context of the white muscle. In fact, at fish body level, it is greater in the anterior area than in the posterior area and in the dorsal area compared to the caudal area.[14] Finally, parvalbumin isoforms have been demonstrated a different allergenic strength.[13]

Parvalbumin has been shown to not be the only known allergen responsible for IgE-mediated fish allergy. In fact, there are minor allergens isolated from the skin and the muscle tissue of the fish.[2] Specifically, they are the vitellogenin hormone, β-enolase and aldolase enzymes, collagen and gelatine.[2]

In light of the above information, the diagnosis of IgE-mediated food allergies is based on the patient's medical history, on the skin prick test (SPT) and with *in-vitro* quantification of IgE antibodies (sIgE) directed against fish proteins.[2] Specifically, the SPT is characterized by a high negative predictive value and a low positive predictive value.[15] At the same time, the limitation of *in-vitro* skin allergy tests is that patients who generate IgE antibodies against a specific parvalbumin often react also to parvalbumin of other fish species. It demonstrates the importance of parvalbumin as the main allergen implicated in the phenomenon of cross-reactivity within this type of allergy.[2, 15] In addition, the parvalbumin present in the various fish species varies considerably and it may seem that a greater amount of parvalbumin, within a given fish species, is related to a greater allergenic power.[16] Specifically,

at molecular level, the allergenic cross-reactivity among the most common species of fish, it has been proved how the recombinants of cod, yellow turbot, salmon, herring and wolf fish contain the most powerful cross-reactive allergens; on the other hand, halibut, plaice, tuna and mackerel represent the species of fish containing allergens with less allergenic power.[17] On the contrary, a correlation between the plasma concentration of sIgE relative to the different fish species and the presence of allergy to the relative species has not been demonstrated. In other words, *in-vitro* cross-reactivity and its clinical expression are not related in clinical practice.[18] Given these diagnostic problems, the cases reported in the literature with mono-sensitization to a single fish species are not surprising.[2, 19] This aspect makes the diagnosis of food allergy to fish very complex, it is estimated that a positive predictive value is often less than 50% for *in-vitro* and *in-vivo* diagnostic tests, when used alone.[15] At the present time, as for all the IgE mediated food allergies, the gold standard for certainty of diagnosis is represented by the double-blind oral food challenge, which has to be performed in a clinical setting.[2, 20] Once diagnosed, the management of IgE-mediated food allergy mediated to fish is generally aimed at avoiding fish believed to be attributable to an allergic reaction at the end of the diagnostic process. This is added to the rapid recognition and treatment of any acute allergic reactions, including those allergic reactions following the inhalation of cooking steam.[2, 21] There are basically two reasons for this therapeutic conduct: first, the possible cross-reactivity between the various parvalbumin; second, the lack of ease of distinction between some fish when ingested.[2, 22] Also in pediatric age, the diagnosis of allergy to fish is common before the age of 2, often coinciding with the first intake of a fish species in the diet.[2] In such cases, the rigorous exclusion of fish from the diet is necessary and, subsequently, it has to be performed a specific diagnostic procedure in a clinical setting, aimed at the progressive reintroduction in the diet of some fish species, starting from those with a greater possibility of food tolerance.[2] Given the specific cross-reactivity between the different fish species, linked to the peculiarities of parvalbumin, this diagnostic procedure would consist in subjecting the patient to SPT and sIgE dosage to multiple species of fish and/or different fish preparations, with a subsequent oral food challenge for fish species, whose diagnostic tests were negative.[23] In any case, until the tolerance to a specific fish species is confirmed, its intake must be prohibited in the diet.[2] Still embryonic is the field of scientific research directed towards the definition of an oral immunotherapy for fish, as happens, on the contrary, in some specialized centres for milk, egg and peanuts.[2]

Regarding the prognosis, allergy to fish tends to be persistent, 65.5% of children affected by sensitization to fish allergens maintain their sensitization throughout their lives.[24]

In light of the above information, it is possible to look a new insight on diagnosis and management of IgE-mediated fish allergy in children, considering the use of canned tuna in clinical settings.

Literature search

Authors performed a systematic literature search through the Cochrane Library and Medline/PubMed databases. All quantitative and qualitative pediatric studies involving diagnosis and management of IgE-mediated fish allergy and the use of canned tuna in clinical settings were considered. Articles related to allergological and nutritional features of fish, and especially canned tuna, were selected. This research was conducted on May 2020.

Canned tuna – allergological considerations

IgE mediated fish allergy is not universal.[23] Clinical experience has shown that the patients suffering from IgE-mediated fish allergy could tolerate some species of fish, which can be reintroduced in the diet of an allergic child to a specific type of fish, by verifying their tolerance with a oral food challenge in a clinical setting.[20] As explained beforehand, this phenomenon finds its explanation in the aforementioned peculiar characteristics of the parvalbumin protein.[9-14] Although clinical experience has led to a further result in the

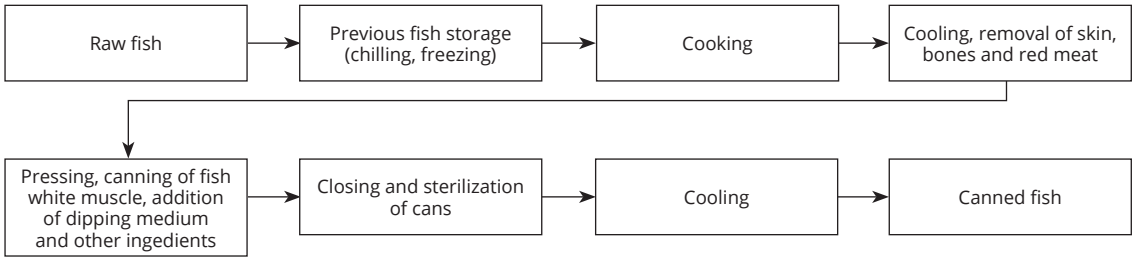

Figure 1.—Production process of canned tuna.

diagnostic process of IgE mediated food allergy to fish, the canning of the fish itself can alter the allergenicity of this protein.[11, 12] Considering that about 30% of fish products are consumed in the canned form in developed countries, this aspect has a very important connotation.[25] Little evidence is available in this area, in particular regarding canned tuna. Specifically, descriptive studies based on small population cohorts have estimated that more than 20% of patients, both in pediatric and adult age, suffering from IgE-mediated food allergy to fish and with an initial reaction against non-canned fish species, can tolerate fish in the corresponding canned form.[26]

In a study of 18 patients, both in pediatric and adult age, suffering from IgE-mediated fish allergy, all patients were able to tolerate canned tuna.[27] On the contrary, there are descriptive studies involving small cohorts and case series that describe sporadic cases of failure to the tolerance of canned fish.[26, 28] Regarding the diagnostic tests, there does not seem to be a correlation between the diameter of the SPT with fish extract or prick-prick with canned tuna and the outcome of the oral food challenge.[26] Therefore, at the present time, the correct therapeutic procedure involves avoiding even canned fish in the diet in patients suffering from IgE-mediated fish allergy, with the need to evaluate its possible reintroduction into the diet itself only through oral food challenge.[26]

The pathophysiological explanation of cases of canned tuna tolerance in subjects suffering from IgE mediated fish allergy is due to the fact that parvalbumin protein has been shown to be a thermo-stable protein, not degradable by heat or by gastric processing.[9, 10, 12-14] There is however evidence that the canning process, characterized by cooking the fish under pressure for a time equal to about 7 hours, could lead to a conformational change in parvalbumin, making it less allergenic.[11, 12] Specifically, when the fish is caught, a refrigeration process is necessary to allow an adequate conservation of the raw fish.[29] Once the raw fish arrives in the factory, it is goes to a cooking phase with the aim of reducing humidity and deactivating the enzymatic activity present in the fish itself, which would lead to the putrefaction of the same. Once this cooking process is completed, a further rigorous heat treatment is carried out aimed at sterilizing the product with the purpose of inactivating the microorganisms present. Finally, adequate storage in boxes is important in order to guarantee a good palatability of the product (Figure 1).[29, 30] It is therefore deducible that, historically, the tuna canning was not aimed at creating a product with less allergenicity, but rather at using a fish product that is easy to preserve and long-lasting thanks to the permanent inactivation of enzymes and bacteria through the various stages of the boxing process.

Canned tuna – nutritional considerations

In the exclusion diet used in the management, the IgE-mediated fish allergy could lead the pediatric patient to nutritional deficiencies.[31] Consequently, it is necessary for this exclusion diet to be accompanied by the intake of foods with an adequate nutritional profile, with the aim for the patient to introduce a healthy and balanced diet.[31] Fish has an important nutritional value: it is rich in B, D and A vitamins, iodine and omega-3.[31] While vitamins are found in the diet from other animal and vegetable foods and iodine is now commonly added to table salt, omega-3 is present

in a few other non-fish foods, such as vegetable seed oils (especially flax seeds) and nuts.[32] The term "omega-3" refers to a group of essential long chain fatty acids and very long chain poly-unsaturated fatty acids.[32] They are taken through the diet and not endogenously synthesized.[32] They are embedded in cell membranes and play a key role in regulating inflammatory processes. A recent review of the literature recommends omega-3 supplementation in children with fish allergy.[31] Its effects would seem to have a positive impact on cognitive development, visual acuity, cardiovascular health and modulation of the immune system.[31, 33] Observational studies showed in subjects suffering from autism spectrum disorders, Attention Deficit Hyperactivity Disorder (ADHD) and paediatric psychosis, plasma deficiency of omega-3.[34] Omega-3 together with omega-6 fatty acids and arachidonic acid, perform various functions in the process of neurogenesis, neurotransmission and protection against oxidative stress.[34] It has been shown that omega-3 supplementation appears useful as support therapy in neuropsychiatric disorders.[34] Regarding omega-3 supplementation in healthy subjects, the evidences are contrasting. Newberry *et al*. has shown that the supplementation of omega-3, omega-6 and arachidonic acid in pregnant or lactating women (or the use of a milk formulated and enriched with these micronutrients) does not bring a significant benefit both during pregnancy and during childhood.[35] In particular, no significant effects of this integration emerged regarding reduction of gestational hypertension and/or peripartum depression, ADHD, learning disorders and visual acuity, cognitive development and prevention of both allergic diseases and asthma in children.[34] Although, a meta-analysis conducted by Papamichael *et al.* has shown that the introduction of fish early in life (6-9 months) and a regular consumption of fish (at least once a week) reduces the incidence of acute wheezing episodes in children up to 4-5 years of age.[35] Based on these considerations, the current state is represented by recommending an omega-3 supplementation to patients in paediatric age, suffering from an IgE-mediated allergy to fish and in a fish exclusion diet.[30] At the same time, we did not find studies in the literature that investigate the long-term outcome of children suffering from a fish-based IgE food allergy and placed on an exclusion diet, with the absence of an adequate nutritional replacement of omega-3.[36]

Regarding the possibility of using canned fish in the diet of a patient suffering from a fish-based IgE food allergy, it assumes an almost historical connotation the consideration that, in the same way in which parvalbumin changes its allergenic connotation during the processing of fish, this procedure can also alter the nutrients present in it (proteins, vitamins, lipids, minerals) and, therefore, it can alters the nutritional and sensory values of the canned final product.[29] The reason for this consideration lies in the fact that studies carried out in the past have shown how this alteration of the canned product derives from the fact that all the processes involved in the canning of the fish (to a greater extent, the prolonged cooking phase) lead to the formation of numerous metabolites, which can interact with the macromolecules present in fish (especially proteins), generating a loss in the quality of these macromolecules and, in general, in the quality of the final product.[29] In recent years, fish processing and canning techniques have been perfected, especially in the heat treatment phase, avoiding the loss in quality of the final product, providing that the raw material used is of high quality.[29]

Another critical issue for the consumption of canned fish in the diet is represented by the presence of mercury in fish, the levels of which in food are established by government which regulate the controls carried out during all the phases preceding the commercialization of the same.[37, 38] The regulation became necessary after the publication of evidences showing that a repeated exposure to high levels of mercury in the prenatal period can be associated with long-term cognitive deficits.[39] In particular when mercury is released as a gas from the earth's crust and from the oceans or as a chemical by-product of the industry, it dissolves in the water, where the bacteria transform it into methylmercury, which the fish absorb.[37] Regarding the pediatric age, the FDA has classified the various fish species based on the concentration of mercury contained therein; specifically, almost all canned tuna species have been indicated as "good choice," authorizing the consumption

of 28 grams and 28-56 grams per week of this particular fish category in children aged less or more than 2 years respectively.[37, 38] In fact, the risk/benefit ratio appears to be disadvantageous in eliminating fish from the diet for fear of assuming mercury. Recent studies have highlighted the possible presence of additional potentially toxic components within the fish. Specifically, with regards to the canned tuna available on the market, the average concentration of arsenic, lead, mercury, zinc, chromium, iron, copper and nickel is lower than the normal limits, while the average concentrations of cadmium and selenium are higher than those values.[40] Despite this, it has been shown that these concentrations of cadmium and selenium are not associated with a carcinogenic risk.[40] However, no studies have been carried out on possible subsequent consequences to the chronic exposure to these components in children.[40] The same safety profile of fish consumption has also been demonstrated with regard to the possible presence of organic contaminants, such as persistent organic pollutants, polychlorinated biphenyls and dioxins.[41] The American Academy of Pediatrics itself, in the context of its study groups responsible for environmental health and nutrition, has expressed itself on the presence of a favorable and significantly sustainable nutritional profile for the consumption of fish, including canned fish, in the pediatric age diet.[41] Despite this, pediatric subjects have a low consumption of fish and especially canned tuna, with a gradually decreasing trend over the years.[41] Overall, for the majority of commercially available wild and farmed species, it would appear that the health benefits, represented by the decreased risk of cardiovascular disease and positive effect on infant neurodevelopment potential, outweigh potential risks given by the presence of mercury and organic pollutants.[41]

Conclusions

IgE-mediated fish allergy is not universal.[23] Consequently, the diagnostic process of an IgE-mediated allergy to fish is aimed at the progressive reintroduction of some fish species into the diet, starting with those with a greater possibility of food tolerance.[2] Canned tuna would represent a solution with an excellent risk/benefit ratio both from an allergological and nutritional point of view. Tuna is mainly made up of red muscle, thus containing a smaller amount of parvalbumin, which is, instead, contained in the white muscle of the fish.[11, 12] It shares this characteristic with the swordfish, which however does not share the characteristic of being subjected to processing and canning, with the result of leading to a conformational change in the parvalbumin itself, making it less allergenic.[11, 12] From a nutritional point of view, canned fish contains vitamins of the group B, D and A and, above all, omega-3 fatty acids, especially *Eicosapentaenoic Acid* (EPA) and *Docosahexanoic Acid* (DHA), even though the content of the latter changes depending on the species and seasons of the year in to which they are fished.[37] These characteristics of lower allergenicity and the adequate nutritional value are associated both with its rich availability in supermarkets at reasonable costs, making it accessible also for consumers of socially disadvantaged groups, and with the ease of transport and storage of cans. Ultimately, the consumption of canned tuna could improve the quality of life of the child suffering from fish allergy and his parents, avoiding an absolutely restrictive dietary conduct for fish. However, the current evidence is limited, as represented by descriptive studies involving small population cohorts in pediatric and adult age; there are also no randomized controlled trials on canned tuna tolerance in subjects suffering from IgE mediated allergy in children. Consequently, the only way to resort to a possible introduction of canned tuna in the dietary scheme of these subjects is represented by the oral food challenge in a clinical setting. In fact, despite the peculiar biochemical characteristics of parvalbumin and a substantially safe profile of canned tuna in the context of the descriptive studies presented, a home reintroduction of canned tuna into the diet of subjects suffering from IgE mediated allergy in children, would appear risky. It is necessary that scientific research in the field of IgE-mediated fish allergy must be aimed at simplifying the diagnostic classification of this particular type of food allergy, which is probably, at the diagnostic level, the most complicated in the field of food allergies in pediatric age.

References

1. Connett GJ, Gerez I, Cabrera-Morales EA, Yuenyongviwat A, Ngamphaiboon J, Chatchatee P, *et al.* A population-based study of fish allergy in the Philippines, Singapore and Thailand. Int Arch Allergy Immunol 2012;159:384–90.

2. Sharp MF, Lopata AL. Fish allergy: in review. Clin Rev Allergy Immunol 2014;46:258–71.

3. Elsayed SM, Aas K. Characterization of a major allergen (cod.) chemical composition and immunological properties. Int Arch Allergy Appl Immunol 1970;38:536–48.

4. Bugajska-Schretter A, Elfman L, Fuchs T, Kapiotis S, Rumpold H, Valenta R, *et al.* Parvalbumin, a cross-reactive fish allergen, contains IgE-binding epitopes sensitive to periodate treatment and Ca2+ depletion. J Allergy Clin Immunol 1998;101:67–74.

5. Lim DL, Neo KH, Yi FC, Chua KY, Goh DL, Shek LP, *et al.* Parvalbumin—the major tropical fish allergen. Pediatr Allergy Immunol 2008;19:399–407.

6. Yoshida S, Ichimura A, Shiomi K. Elucidation of a major IgE epitope of Pacific mackerel parvalbumin. Food Chem 2008;111:857–61.

7. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010;125(Suppl 2):S116–25.

8. Lopata AL, Lehrer SB. New insights into seafood allergy. Curr Opin Allergy Clin Immunol 2009;9:270–7.

9. Bannon GA. What makes a food protein an allergen? Curr Allergy Asthma Rep 2004;4:43–6.

10. Moreno FJ. Gastrointestinal digestion of food allergens: effect on their allergenicity. Biomed Pharmacother 2007;61:50–60.

11. Tuna Processing Industry. United States Department of Labor; 2020 [Internet]. Available from: http://www.dol.gov/whd/AS/sec3.htm [cited 2020, May 17].

12. Kuehn A, Swoboda I, Arumugam K, Hilger C, Hentges F. Fish allergens at a glance: variable allergenicity of parvalbumins, the major fish allergens. Front Immunol 2014;5:179.

13. Kobayashi A, Tanaka H, Hamada Y, Ishizaki S, Nagashima Y, Shiomi K. Comparison of allergenicity and allergens between fish white and dark muscles. Allergy 2006;61:357–63.

14. Lim DL, Neo KH, Goh DL, Shek LP, Lee BW. Missing parvalbumin: implications in diagnostic testing for tuna allergy. J Allergy Clin Immunol 2005;115:874–5.

15. Lee LA, Burks AW. Food allergies: prevalence, molecular characterization, and treatment/prevention strategies. Annu Rev Nutr 2006;26:539–65.

16. Kuehn A, Scheuermann T, Hilger C, Hentges F. Important variations in parvalbumin content in common fish species: a factor possibly contributing to variable allergenicity. Int Arch Allergy Immunol 2010;153:359–66.

17. Van Do T, Elsayed S, Florvaag E, Hordvik I, Endresen C. Allergy to fish parvalbumins: studies on the cross-reactivity of allergens from 9 commonly consumed fish. J Allergy Clin Immunol 2005;116:1314–20.

18. Schulkes KJ, Klemans RJ, Knigge L, de Bruin-Weller M, Bruijnzeel-Koomen CA, Marknell deWitt A, *et al.* Specific IgE to fish extracts does not predict allergy to specific species within an adult fish allergic population. Clin Transl Allergy 2014;4:27.

19. Ebo DG, Kuehn A, Bridts CH, Hilger C, Hentges F, Stevens WJ. Monosensitivity to pangasius and tilapia caused by allergens other than parvalbumin. J Investig Allergol Clin Immunol 2010;20:84–8.

20. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, *et al.* EAACI Molecular Allergology User's Guide. Pediatr Allergy Immunol 2016;27(Suppl 23):1–250.

21. Crespo JF, Pascual C, Dominguez C, Ojeda I, Muñoz FM, Esteban MM. Allergic reactions associated with airborne fish particles in IgE-mediated fish hypersensitive patients. Allergy 1995;50:257–61.

22. Strauss RE, Bond CE. Taxonomic methods: morphology. In: Schreck CB, Moyle PB, editors. Methods for fish biology. Bethesda, MD: American Fisheries Society; 1990. p.109–40.

23. Mourad AA, Bahna SL. Fish-allergic patients may be able to eat fish. Expert Rev Clin Immunol 2015;11:419–30.

24. Priftis KN, Mermiri D, Papadopoulou A, Papadopoulos M, Fretzayas A, Lagona E. Asthma symptoms and bronchial reactivity in school children sensitized to food allergens in infancy. J Asthma 2008;45:590–5.

25. Report on the State of World Fisheries and Aquaculture. Department of Food and Agriculture Organization of the United Nations; 2008 [Internet]. Available from http://www.fao.org/docrep/011/i0250e/i0250e00.htm [cited 2020, May 17].

26. Turner P, Ng I, Kemp A, Campbell D. Seafood allergy in children: a descriptive study. Ann Allergy Asthma Immunol 2011;106:494–501.

27. Bernhisel-Broadbent J, Strause D, Sampson HA. Fish hypersensitivity. II: clinical relevance of altered fish allergenicity caused by various preparation methods. J Allergy Clin Immunol 1992;90:622–9.

28. Kelso JM, Bardina L, Beyer K. Allergy to canned tuna. J Allergy Clin Immunol 2003;111:901.

29. Aubourg SP. Review: Loss of Quality during the Manufacture of Canned Fish Products. Food Sci Technol Int 2001;7:199–215.

30. Mejrhit N, Azdad O, Aarab L. Effect of industrial processing on the IgE reactivity of three commonly consumed Mo-roccan fish species in Fez region. Eur Ann Allergy Clin Immunol 2018;50:202–10.

31. Skypala IJ, McKenzie R. Nutritional issues in food allergy. Clin Rev Allergy Immunol 2019;57:166–78.

32. Tur JA, Bibiloni MM, Sureda A, Pons A. Dietary sources of omega 3 fatty acids: public health risks and benefits. Br J Nutr 2012;107(Suppl 2):S23–52.

33. González FE, Báez RV. In time: importance of omega-3 in children's nutrition. Rev Paul Pediatr 2017;35:3–4. Portuguese.

34. Agostoni C, Nobile M, Ciappolino V, Delvecchio G, Tesei A, Turolo S, *et al.* The Role of Omega-3 Fatty Acids in Developmental Psychopathology: A Systematic Review on Early Psychosis, Autism, and ADHD. Int J Mol Sci 2017;18:2608.

35. Newberry SJ, Chung M, Booth M, Maglione MA, Tang AM, O'Hanlon CE, *et al.* Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review. Evid Rep Technol Assess (Full Rep) 2016;(224):1–826.

36. Papamichael MM, Shrestha SK, Itsiopoulos C, Erbas B. The role of fish intake on asthma in children: A meta-analysis of observational studies. Pediatr Allergy Immunol 2018;29:350–60.

37. Cassel P. FDA In Brief: FDA revises 2017 fish advice for pregnant and breastfeeding mothers and young children. FDA; 2019 [Internet]. Available from: https://www.fda.gov/news-events/fda-brief/fda-brief-fda-revises-2017-fish-advice-pregnant-and-breastfeeding-mothers-and-young-children [cited 2019, May 17].

38. Advice about eating fish. FDA; 2019 [Internet]. Available

from: https://www.fda.gov/food/consumers/advice-about-eating-fish [cited 2019, May 17].

39. Debes F, Weihe P, Grandjean P. Cognitive deficits at age 22 years associated with prenatal exposure to methylmercury. Cortex 2016;74:358–69.

40. Rahmani J, Fakhri Y, Shahsavani A, Bahmani Z, Urbina MA, Chirumbolo S, *et al*. A systematic review and meta-analysis of metal concentrations in canned tuna fish in Iran and human health risk assessment. Food Chem Toxicol 2018;118:753–65.

41. Bernstein AS, Oken E, de Ferranti S; COUNCIL ON ENVIRONMENTAL HEALTH; COMMITTEE ON NUTRITION. Fish, Shellfish, and Children's Health: An Assessment of Benefits, Risks, and Sustainability. Pediatrics 2019;143:e20190999.

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