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Summary of Health Canada's assessment of a health claim about eicosapentaenoic acid, docosahexaenoic acid and triglyceride lowering

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Background

In November 2013, Health Canada's Food Directorate received an application for a therapeutic claim about eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and triglyceride lowering. The information below is a summary of Health Canada's review based on the *Guidance Document for Preparing a Submission for Food Health Claims*.

In 2010, Health Canada reconsidered the classification of food products with disease risk reduction claims or therapeutic claims in light of clarified principles for the classification of foods at the Food-Natural Health Product interface. Health Canada's position is that when food products are marketed for a disease risk reduction or therapeutic benefit, which comes as a result of the food's normal use as part of the diet, these products may be classified and regulated as foods. In other words, the use of a disease risk reduction claim or a therapeutic claim alone is not sufficient to classify the product as a natural health product.

Scientific evidence supporting the claim

The foods that are the subject of the health claim are foods containing eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA). EPA and DHA are long-chain omega-3 fatty acids with lipid structures of 20:5(n-3) and 22:6(n-3), respectively.

The petitioner provided a literature search covering a period up to September 2012 to substantiate the proposed health claim. The literature search was updated by Health Canada's Food Directorate to encompass studies published to September 2014. References were included if they reported on randomized intervention studies or prospective observational studies; included a suitable control group; included at least 5 subjects; included generally healthy and non-medicated adults (≥18 years of age); administered 5 g/day or less of EPA+DHA without co-administering another treatment known to affect blood lipids; lasted a minimum of 4 weeks (+ 4 week washout for crossover studies); reported changes in fasting triglyceride levels; and reported on statistical significance between groups. A total of 77 relevant references, comprising 108 relevant treatment arms and 1 observational study were identified [1-77].

Of the 77 relevant studies, 59 were parallel studies, 17 were crossover studies and one was a prospective observational study [6]. Sample sizes among parallel studies ranged from 15 to 274, while it ranged from 6 to 312 in the crossover studies. The observational study analyzed the data of 1689 men.

The studies were conducted in healthy or non-medicated hyperlipidemic males and females. Ages at baseline ranged from 18 to 85 years. Studies were carried out in Europe, America, Oceania, Asia and Africa. The intake of EPA+DHA ranged from 0.013 g/day to 5 g/day. Treatment duration ranged from 4 to 26 weeks for the clinical trials. The follow-up of the observational study lasted 4 years.

EPA and/or DHA were consumed from supplements in 54 studies, from fortified foods in 10 studies and from fish in 14 studies. One study used supplements for some trial arms and fish for other trial arms [53]. Supplements were mainly capsules containing fish oil, krill oil, seal oil or algal oil while fortified foods included milk, soy milk, yoghurt, cheese, cheese spread, butter, margarine, shortening, biscuits, bread, pancakes, muffins, chocolate, instant oats, dips, salad dressing, dry soup mix, eggs and pork. A variety of fish species were consumed in the studies including trout, herring, salmon, mackerel, tuna and sardines.

The outcome considered is fasting triglycerides levels (TG). A fasting plasma or serum triglyceride concentration greater than 1.7 mmol/L is considered unhealthy and is one of the defining characteristics of metabolic syndrome [78].

The direction of effect was highly consistent (89% of treatment arms) towards a reduction in triglyceride levels with EPA and DHA consumption. However, a low proportion of studies showed a statistically significant reduction in triglyceride levels (50%). These conclusions were similar when only higher quality studies were taken into account.

Similar results were observed when treatment arms were grouped by method of consumption of EPA+DHA (supplements, fortified foods or fish), except that for the subgroup of fortified foods the direction of effect was slightly less consistent (67%) and a lower proportion of studies showed a statistically significant reduction in triglyceride levels (25%). This could be due to the lower doses of EPA+DHA used in the studies administering EPA+DHA from fortified foods.

When only studies with at least 30 participants and administering a daily intake of EPA+DHA of at least 1.5 g or 2 g were taken into account, a large proportion of studies showed a statistically significant reduction in triglyceride levels (82% and 88% of treatment arms, respectively). These studies were all of higher quality.

A daily intake of 1.5 g of EPA+DHA was chosen as the minimum effective intake because the vast majority (>80%) of the treatment arms from the larger studies (≥30 participants) administering a daily intake of at least 1.5 g of EPA+DHA demonstrated a statistically significant reduction in triglyceride levels. This was also the case for the treatment arms from the larger studies administering a daily intake of at least 2 g of EPA+DHA. A minimum effective intake of 1 g/day was not retained because none of the 4 treatment arms from higher quality and larger studies (≥30 participants) administering between 1 g/day and 1.5 g/day of EPA+DHA showed a statistically significant reduction in triglyceride levels [50, 54, 59, 76]. Two of these 4 studies are especially relevant to the claim since either fish [76] or foods fortified with EPA and DHA were consumed [54].

The EPA:DHA ratio in the studies showing a statistically significant reduction in triglyceride levels ranged from 0:1 to 1:0. Therefore, no minimum and maximum ratios have been established for this claim.

The reduction of triglyceride levels with the consumption of EPA and/or DHA ranged from -48% to -3% (-1.52 to -0.02 mmol/L) in the treatment arms from larger studies (n≥30) administering a daily intake of at least 1.5 g of EPA+DHA. The mean triglyceride reduction among these treatment arms was -23% (-0.39 mmol/L). This effect is consistent with other systematic reviews investigating the effect of EPA and DHA on triglyceride levels [79, 80]. Reductions in triglycerides of 20% to 24% and in the range of 20% to 50% have been respectively described as "substantial reductions" [81] and as a "marked triglyceride-lowering effect" [82].

Results from the observational study are consistent with the results from the clinical trials: the odds ratio of having high triglyceride levels was lower (0.54; 95% CI 0.34 to 0.86) in men eating fish daily than in men eating less than one serving of fish per week [6].

Health Canada's Food Directorate conclusion

The evidence consistently supports a highly consistent direction of effect towards a reduction in triglyceride levels when EPA and DHA are consumed. The vast majority (>80%) of the treatment arms from the larger studies (≥30 participants) administering a daily intake of at least 1.5 g of EPA+DHA demonstrated a statistically significant reduction in triglyceride levels.

Health Canada's Food Directorate has concluded that scientific evidence exists to support a claim about EPA+DHA and triglyceride lowering. The claim is relevant and generally applicable to the Canadian adult population on the basis that approximately 25% of Canadian adults aged 20 to 79 had unhealthy triglyceride levels[1] (>1.7 mmol/L) from 2007 to 2009.

[1] Statistics Canada. 2010. Heart health and cholesterol levels of Canadians, 2007 to 2009. http://www.statcan.gc.ca/pub/82-625-x/2010001/article/11136-eng.htm [last accessed on June 4, 2015].

Health claim

The following statements may be made in the labelling and advertising[2] of food products meeting the qualifying criteria.

Primary statement[3]*:*

> [*serving size from Nutrition Facts table in metric and common household measures*] of (*brand name*) [*name of food*] supplies/provides X% of the daily amount of (long-chain) omega-3 (fatty acids) EPA[4] and DHA[5] shown to help reduce/lower triglycerides.

For example[6]:

> 85 g (½ cup) of canned pink salmon supplies 40% of the daily amount of omega-3 EPA and DHA shown to help lower triglycerides.

The "daily amount" referred to in the primary statement is 1.5 g of EPA+DHA. This amount is based on the evidence available concerning the amount of EPA+DHA shown to help reduce triglyceride levels. In this statement, the percentage of the daily amount of EPA+DHA provided in one serving should be rounded to the nearest multiple of 5%.

Additional statements[3]*:*

The following additional statement may be placed adjacent to the primary statement, in letters up to twice the size and prominence of those in the primary statement:

> (Long-chain) (omega-3) EPA and DHA help reduce/lower triglycerides

[2] The information in this document complements the labelling information published by the Canadian Food Inspection Agency. It is the responsibility of all manufacturers and importers to ensure that their products comply with all relevant Canadian legislation and regulations.
[3] [ ] = mandatory; ( ) = optional; / = acceptable alternate wording
[4] "eicosapentaenoic acid" could be used in replacement of EPA
[5] "docosahexaenoic acid" could be used in replacement of DHA
[6] Examples are for illustration purposes only. They do not necessarily reflect acceptable health claims.

Conditions for foods to carry the claim

The following qualifying criteria apply to all food products carrying the above-mentioned health claim.

The food:

a) contains at least 0.5 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) combined
   i. per reference amount and per serving of stated size, or
   ii. per serving of stated size, if the food is a prepackaged meal, a nutritional supplement or a meal replacement;
b) contains at least 10% of the weighted recommended nutrient intake (WRNI) of a vitamin or mineral nutrient
   i. per reference amount and per serving of stated size, or
   ii. per serving of stated size, if the food is a prepackaged meal, a nutritional supplement or a meal replacement;
c) contains 0.5% or less alcohol;
d) contains
   i. less than 15% of the Daily value (DV) of sodium per reference amount and per serving of stated size, and per 50 g if the reference amount is 30 g or 30 mL or less, or
   ii. less than 15% of the Daily value (DV) of sodium per serving of stated size, if the food is a nutritional supplement or a meal replacement, or
   iii. less than 25% of the Daily value (DV) of sodium per serving of stated size, if the food is a prepackaged meal;
e) contains
   i. less than 15 g of total sugars per reference amount and per serving of stated size, or
   ii. less than 15 g of total sugars per serving of stated size, if the food is a prepackaged meal, a nutritional supplement or a meal replacement;
f) is not one of the types of fish for which Health Canada recommends limiting consumption, due to their mercury concentrations, that is, fresh and frozen tuna, shark, swordfish, escolar, marlin, orange roughy and canned albacore (white) tuna.

Conditions for the label and advertisement

- If the statement or claim is made on the label of or in the advertisement for a prepackaged product by or on the direction of the manufacturer of the product, the Nutrition Facts table shall include the amount of monounsaturated fats, as well as omega-3 and omega-6 polyunsaturated fatty acids in accordance with subsection B.01.402(2).

- If the statement or claim is made on the label of or in the advertisement for a food that is not a prepackaged product, or in the advertisement for a prepackaged product that is not made or placed by or on the direction of the manufacturer of the product, the label or advertisement shall include the amount of monounsaturated fats, as well as omega-3 and omega-6 polyunsaturated fatty acids per serving of stated size, in accordance with the intent of the requirements for print, radio and television advertisement set out in section B.01.602.

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