Original Article

The Benefit Risk Assessment of Consumption of Marine Species Based on Benefit-Risk Analysis for Foods (BRAFO)-tiered Approach*

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Abstract

Objective To assess the net health effect caused by the consumption of specific marine species based on Benefit-Risk Analysis for Foods (BRAFO)-tiered approach.

Methods Twenty species were collected from the Zhoushan Archipelago, China. Concentrations of n-3 long-chain polyunsaturated fatty acids, methyl mercury (MeHg), and dioxin-like compounds (DLCs) in the samples were analyzed for benefit risk assessment based on BRAFO-tiered approach.

Results Based on the BRAFO-tiered approach, reference scenario (no intake) and alternative scenario (intake of specific species of 200 g/week) were determined. The exposure to MeHg/DLCs via alternative scenario of all studied species did not exceed provisional tolerable weekly/monthly intake. However, the adult population with high DLCs exposure in China would significantly exceed the upper limit of DLCs via an additional alternative scenario of some species such as *Auxis thazard*. The results of deterministic computation showed that alternative scenario of all studied species generated clear net beneficial effects on death prevention and child IQ gain.

Conclusion The alternative scenario of all studied species could be recommended to population with average DLCs exposure, and the reference scenario of species with relatively high DLCs concentration could be recommended to population exposed to high DLCs.

Key words: N-3 long-chain polyunsaturated fatty acid; Methyl mercury; Dioxin-like compound; Benefit-Risk Analysis for Foods (BRAFO); Benefit risk assessment

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INTRODUCTION

Aquatic foods, particularly marine species, are a good dietary source of n-3 long-chain polyunsaturated fatty acids [n-3 LCPUFAs, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)]. These fatty acids are known to be beneficial to adult cardiovascular system[1], infant neural and visual development[2], and immune system[3]. However, the

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marine species also contain chemical contaminants, and the consumption of marine species is the major pathway by which general population is exposed to them, such as methyl mercury[4-5], which would increase risk of adult myocardial infarction[6] and be adverse to children neurodevelopment[7]. Dioxin-like compounds (DLCs) are another type of chemical contaminants in aquatic foods[8], which could cause cancers, diabetes, and cardiovascular disorder in the exposed population[9]. These aforementioned facts indicate that increase in consumption of marine species would simultaneously increase the exposure to both beneficial and adverse effects. Therefore, it is necessary to weigh the benefits and risks and assess the net health effect caused by consumption of aquatic foods.

Some approaches for benefit-risk assessment have been proposed as a response to the public health issue. 'risk benefit index (RBI) equations' is a quantitative method that integrates the potential risks and benefits caused by consumption of MeHg and n-3 LCPUFAs based on known dose-response relationships[10]. A study on wild fish consumption in Alaska based on RBI equations showed that consistent consumption advice of specific species would be difficult to craft because the net effects calculated by RBI equations were significantly variational among regions or studies within the same region[11]. The conclusions derived from the RBI equations could be tentative because of the 'uncertainties in the underlying dose response'[10]. The authors considered that their focus was 'the potential utility' of the equations rather than the obtainment of exact results, and their analysis showed 'key research areas for improving risk/benefit analysis for fish consumption'[10].

The net health effect caused by consumption of nine freshwater fish species from Taihu Lake was assessed in a recent Chinese study based on 'allowable daily consumption', which was proposed by the US Environmental Protection Agency[12]. The study showed that the consumption of these species would not exceed the allowable daily consumption of polychlorinated biphenyls (PCBs) when the recommended intake amount of EPA plus DHA (250 mg/d[1]) was achieved. However, there were no data regarding MeHg concentration in the studied species, and the net cardiovascular effect caused by the consumption of specific species was the only considered factor in that study.

'Quality-adjusted life year (QALY)' was also proposed to assess the net health effect of fish consumption based on which some studies indicated that an increase in fish consumption, particularly the fish with low MeHg concentration, would be beneficial to adult cardiovascular system and prenatal neurodevelopment[13-14]. However, another study based on QALY indicated that fish consumption would cause ambivalent health impact on different target populations with a range of fish MeHg concentrations and consumption amounts[15]. QALY was recommended as a common metric to integrate benefits and risks by a recent project funded by the European Commission: Benefit-Risk Analysis for Foods (BRAFO), of which the aim is to develop a tiered approach for benefit risk assessment of consumption of foods/food compounds[16]. According to a case study on the consumption of farmed salmon based on the BRAFO-tiered approach, the alternative scenario (200 g/week) rather than the reference scenario (no intake) could be recommended because the benefit of the alternative scenario outweighed its risk to population with average DLCs exposure at tier 1; however, it also pointed out that uncertainties existed and the assessment could not advance to tier 3 for population exposed to high DLCs because of lack of data[17].

FAO and WHO held an expert consultation on the risks and benefits of fish consumption, during which the quantitative integration of the health effects caused by consumption of n-3 LCPUFAs, MeHg, and DLCs was summarized[18]; furthermore, this could be applied in the BRAFO-tiered approach as a method for deterministic computation (tier 3).

Although food safety issues are drawing much attention in China, there is little information about the benefit risk assessment of the consumption of China's aquatic foods. Therefore, we assessed the net health effect caused by consumption of some marine fish grown in a fishing ground in southeast China based on the BRAFO-tiered approach to determine the probable recommendation for consumption of specific marine species for Chinese population.

MATERIALS AND METHODS

Sample Collection and Preparation

Twenty locally grown marine species (represented by scientific names in this study) were collected from the Zhoushan Archipelago, China. The samples with medium size (six samples/species, one individual fish/sample) were purchased from the local piers/markets between September and October, 2011.

The edible part of each sample was prepared by collectors. Each processed sample was divided into two parts: one part was a sample of individual fish for further analysis of the concentrations of specific fatty acids and MeHg, and the other parts of three samples belonging to the same species were selected randomly out of six samples of the species and then were mixed equivalently as a pooled sample for further analysis of the concentration of DLCs. This implied that each species had six samples for specific fatty acids and MeHg analysis and one pooled sample for DLCs analysis. All samples were frozen at -20 °C until analysis.

Sample Analysis

Information on analysis of specific fatty acids by gas chromatography with flame ionization detector has been described in published articles[19-20]. The oven program had an initial temperature of 60 °C (held for 5 min), which was subsequently increased to 165 °C at a rate of 5 °C/min, when there was an one-minute isothermal period, followed by 1 °C/min to 193 °C (held for 25 min), and then 2 °C/min to 225 °C (held for 15 min).

MeHg in the sample was separated by liquid chromatography with RP C_{18} column and then the concentration was determined by non-dispersive atomic fluorescence spectrometer[4].

DLCs in the pooled sample were analyzed by high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS)[21]. DLCs contain dioxins and dioxin-like PCBs in this study.

Benefit Risk Assessment Methodology

The BRAFO-tiered approach was applied to assess the net health effect caused by consumption of the studied species, which consists of five steps: 1) pre-assessment and problem formulation, which include setting the scope of the assessment and describing the benefits and risks potentially involved in particular consumption scenarios (i.e., reference scenario and alternative scenario); 2) individual assessment of risks and benefits (tier 1), of which the objective is to identify the health effects caused by beneficial and risk factors individually in the case of change from reference scenario to alternative scenario; 3) qualitative integration of risks and benefits (tier 2), in which the benefits and risks caused by scenarios would be characterized based on the severity of the effects and on the potential number of individuals affected; 4) deterministic computation of common metric (tier 3), in which the benefits and risks are compared quantitatively by a common metric; and 5) probabilistic computation (tier 4), during which probability distribution is generated and the net health effect caused by all quantified uncertainties is assessed. According to the BRAFO-tiered approach, if there is a clear net benefit or net risk associated with the alternative scenario compared with the reference scenario in a specific tier, then the benefit risk assessment would stop in the tier and the appropriate scenario would be recommended. More details about BRAFO-tiered approach are available in relevant publications[16-17].

In our study, the FAO/WHO approach will be applied at tier 3 of the BRAFO-tiered approach for deterministic computation if the assessment at this tier is necessary. The mortality and the child IQ were applied as the common metrics for general population and for women of childbearing age, respectively. The equations are listed as follows, and the interpretation of all coefficients in the Equations are described in the FAO/WHO publication[18]:

$$\text{Deaths prevented per million people}=[\text{EPA+DHA}]\times100\times0.36\times110600\times(X/7)\div250 \tag{1}$$

(The maximum positive effect from intake of EPA plus DHA was estimated to occur at 250 mg/day, i.e., the maximum value of '[EPA+DHA]×100×(X/7)' was 250 mg.)

$$\text{Cancer deaths caused per million people}=[\text{Dioxins}]\times100\times(X/7)\div60\times1\times10^{-3}\times10^{6} \tag{2}$$

$$\text{IQ point gain}=[\text{EPA+DHA}]\times100\times0.67\times(X/7)\times0.04 \tag{3}$$

(The maximum positive effect from maternal intake of EPA plus DHA was estimated at 5.8 IQ points.)

$$\text{IQ point loss}=[\text{MeHg}]\times100\times(X/7)\div60\times9.3\times(-0.18\text{ or }-0.7) \tag{4}$$

(In this study, we chose -0.7 as IQ points lost per microgram per gram hair mercury for more conservative assessment.)

Combining Equations (1) and (2) gives a relationship between net mortality change and consumption of specific species due to intake of n-3 LCPUFAs and DLCs:

$$\text{Net deaths prevented per million people}=\text{deaths prevented per million people}-\text{cancer deaths caused per million people} \tag{5}$$

Similarly, the relationship between net IQ point gain and consumption of specific species due to intake of n-3 LCPUFAs and MeHg is summarized as follows according to Equations (3) and (4):

Net IQ point gain=IQ point gain-IQ point loss (6)

When the assessment at tier 4 (probabilistic computation) was necessary, Monte Carlo simulation was applied for generation of probability distribution. The simulated sampling was performed 10,000 times (sample size = 6), and the computation was carried out by Statistical Analysis System 9.1 (SAS Institute Inc., Cary, NC, US).

RESULTS

Concentrations of n-3 LCPUFAs, MeHg, and DLCs

The mean concentrations of total lipids, EPA, n-3 docosapentaenoic acid (n-3 DPA), DHA, and MeHg of all studied species and the concentrations of DLCs of partial pooled samples could be obtained from previously published studies (Table 1)[20-21]. There were positive correlations between concentrations of total lipids and specific n-3 LCPUFAs (EPA: r=0.750, P<0.0001; n-3 DPA: r=0.754, P<0.0001; DHA: r=0.725, P<0.0001). It is noteworthy that there were also positive correlations between concentrations of total lipids and MeHg (r=0.402, P<0.0001), and between mean values of total lipid concentration and DLCs concentration in the pooled sample (r=0.653, P=0.0013).

Assessment Based on BRAFO-tiered Approach: Pre-assessment and Problem Formulation

Fish consumption in China is relatively low: data from the '2002 China National Nutrition and Health Survey' showed that the Chinese average consumption of fish (no identification of species) was 24.8 g/standard man-day (slightly lower than 200 g/week). Therefore, no intake was chosen as the reference scenario and intake of 200 g/week of specific species was chosen as the alternative scenario, which are in accord with the scenarios of a previous case study[17].

Our benefit risk assessment was based on the following factors:

Intake of n-3 LCPUFAs via consumption of specific species exerted preventive effect on coronary heart disease (CHD);

Intake of n-3 LCPUFAs via consumption of specific species caused IQ point gain in fetuses/infants;

Exposure to MeHg via consumption of specific species caused IQ point loss in fetuses/infants; and

Exposure to DLCs via consumption of specific species increased the number of cancer deaths.

The reason why our benefit risk assessment was based on these factors has been discussed in FAO/WHO and BRAFO publications[17-18].

Table 1. Concentrations of EPA plus DHA, MeHg, and DLCs in the Edible Part of Studied Species*

Scientific Name	EPA+DHA (mg/100 g Edible Part)		MeHg (μg/kg Edible Part)		DLCs (pg TEQ/g Edible Part)
	x	s	x	s	
Trichiurus lepturus	590.7	57.2	22.8	3.1	0.073
Larimichthys polyactis	758.9	110.8	15.9	2.7	0.150
Collichthys lucidus	181.3	37.1	12.2	0.8	0.011
Pampus chinensis	470.3	93.2	22.4	3.7	0.369
Muraenesox bagio	836.4	175.7	34.8	6.0	0.359
Conger myriaster	893.8	124	40.6	5.2	0.738
Sebastiscus marmoratus	448.9	98.6	39.6	7.2	0.071
Thamnaconus modestus	137.2	40.1	17.2	2.0	0.011
Scomber japonicus	1251.4	146.5	16.4	1.9	0.529
Scomberomorus niphonius	520.9	94.0	27.4	2.7	0.216
Ilisha elongata	733.1	42.8	36.5	6.7	0.109
Miichthys miiuy	453.6	60.3	16.2	1.7	0.101
Sparus macrocephlus	678.8	142	30.5	3.8	0.519
Harpadon nehereus	189.7	32.5	14.1	4.4	0.033
Raja porosa	123.6	36.8	47.6	4.7	0.179
Mugil cephalus	266.3	268	7.7	5.3	0.478
Lateolabrax maculatus	858.5	230.3	21.0	2.8	0.029
Hexagrammos otakii	379.8	24.6	20.6	1.8	0.227
Oplegnathus fasciatus	469.8	20.6	27.7	5.7	0.360
Auxis thazard	2458.2	395.1	122.8	4.9	2.624

Note. *The data of EPA plus DHA and MeHg of all studied species[20] and those of DLCs of partial studied species[21] could be obtained from previously published studies.

Assessment Based on BRAFO-tiered Approach: Individual Assessment of Risks and Benefits (Tier 1)

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established a provisional tolerable weekly intake (PTWI) of 1.6 μg/kg body weight (bw) for MeHg[22] and a provisional tolerable monthly intake (PTMI) of 70 pg TEQ/kg bw for DLCs[18]. Therefore, PTWI and PTMI were applied to assess the adverse effects caused by the change from reference scenario to alternative scenario (60 kg was considered as the bw of an adult[17-18], and 30 days were considered as 1 month in the calculation of PTMI).

Consumers could increase the intake of n-3 LCPUFAs via the alternative scenario of all studied species (Table 2), which indicates that consumers would gain the corresponding benefits derived from n-3 LCPUFAs in terms of cardiovascular system and neurodevelopment[17]. It is noteworthy that the intake amount of n-3 LCPUFAs would increase on an average by approximately 10% via the alternative scenario if n-3 LCPUFAs included n-3 DPA (Table 2). The exposure to MeHg/DLCs via the alternative scenario of all studied species did not exceed the PTWI/PTMI (Table 2). Therefore, assessment at tier 1 suggests that the alternative scenario of all studied species would provide beneficial health effect, while the exposure to MeHg/DLCs would be lower than their safety upper limits. However, all studied species need to be assessed at the next level because of the uncertainties of contaminants according to a case study on the consumption of farmed salmon[17]. For example, data from the '2007 Chinese Total Diet Study' showed that exposure level of DLCs (69.4-75.9 pg TEQ/kg bw/month) of the highly exposed Chinese adult population (P 97.5) was close to PTMI[23], which indicated that the intake of DLCs of the population (P 97.5) would significantly exceeded the PTMI via an additional alternative scenario of some species, such as *Auxis thazard* [the intake of DLCs via an additional alternative scenario of all studied species would not cause an obvious health risk to the adult population with average DLCs exposure (P 50, 15.7-18.4 pg TEQ/kg bw/month[23]) in China].

Table 2. Intake of EPA plus DHA (mg/d), MeHg (μg/kg bw/week), and DLCs (pg TEQ/kg bw/month) via Alternative Scenario

Scientific Name	n-3 DPA*		EPA+DHA		MeHg		DLCs
	x	*s*	*x*	*s*	*x*	*s*	
Trichiurus lepturus	15.6	3.3	168.8	16.3	0.08	0.01	1.04
Larimichthys polyactis	11.5	1.8	216.8	31.7	0.05	0.01	2.14
Collichthys lucidus	1.6	1.9	51.8	10.6	0.04	0.00	0.16
Pampus chinensis	20.5	3.5	134.4	26.6	0.07	0.01	5.28
Muraenesox bagio	24.9	4.3	239.0	50.2	0.12	0.02	5.13
Conger myriaster	37.4	6.3	255.4	35.4	0.14	0.02	10.54
Sebastiscus marmoratus	11.9	3.0	128.3	28.2	0.13	0.02	1.01
Thamnaconus modestus	1.2	1.7	39.2	11.5	0.06	0.01	0.15
Scomber japonicus	24.2	3.1	357.6	41.8	0.05	0.01	7.55
Scomberomorus niphonius	9.9	2.2	148.8	26.9	0.09	0.01	3.08
Ilisha elongata	16.7	1.7	209.4	12.2	0.12	0.02	1.56
Miichthys miiuy	6.8	4.3	129.6	17.2	0.05	0.01	1.44
Sparus macrocephlus	38.8	8.5	193.9	40.6	0.10	0.01	7.41
Harpadon nehereus	0.5	0.7	54.2	9.3	0.05	0.01	0.47
Raja porosa	5.2	1.2	35.3	10.5	0.16	0.02	2.56
Mugil cephalus	24.1	30.5	76.1	76.6	0.03	0.02	6.82
Lateolabrax maculatus	26.4	7.0	245.3	65.8	0.07	0.01	0.42
Hexagrammos otakii	2.9	0.5	108.5	7.0	0.07	0.01	3.25
Oplegnathus fasciatus	24.1	3.7	134.2	5.9	0.09	0.02	5.15
Auxis thazard	23.3	3.3	702.3	112.9	0.41	0.02	37.49

Note. *The concentrations of n-3 DPA of all studied species could be obtained from a previously published study[20].

Assessment Based on BRAFO-tiered Approach: Qualitative Integration of Risks and Benefits (Tier 2)

According to data from 'the Global Burden of Diseases, Injuries, and Risk Factors Study 2010', the age-standardized death rate (per 100,000) of ischemic heart disease (a type of CHD) was 70.1 (95% UI: 57.2-76.0) and this disease caused 948.7 thousand (95% UI: 774.5 thousands-1024.6 thousands) deaths in 2010 in China, which provided over 10% of the total deaths (8303.7 thousand deaths) caused by 231 statistical diseases/injuries[24]. Ischemic heart disease became the second cause of years of life lost among all 25 top causes in 2010 in China, whereas it was only the seventh cause in 1990[24]. Moreover, there seems to be no significant association between the MeHg intake and the risk of CHD[1]. All these findings indicate that CHD is becoming one of the leading causes of death in China and a large population would benefit from the alternative scenario of all studied species because there would be an inverse dose-response relationship between the intake of n-3 LCPUFAs and the mortality caused by CHD[1].

However, prenatal maternal MeHg exposure via the alternative scenario of all studied species may result in an adverse effect on neurodevelopment because it is still controversial whether there is a threshold for developmental effects by MeHg[17], even though maternal intake of n-3 LCPUFAs via the alternative scenario of all studied species would be beneficial to neurodevelopment. Furthermore, the number of adults with high DLCs exposure (P 97.5) affected by an additional alternative scenario of some studied species would be small, but the adverse effects caused by such over-limit exposure would be severe[18]. These findings indicate that it could not be concluded definitely whether the benefits derived from the alternative scenario dominate the risks in this tier. Therefore, assessment in tier 3 level is necessary.

Assessment Based on BRAFO-tiered Approach: Deterministic Computation of Common Metric (Tier 3)

Obviously, the mortality and the child IQ gain caused by the reference scenario (no intake) of all studied species are zero. Therefore, the calculated results of mortality and child IQ gain of the alternative scenario are also the changes from the reference scenario to the alternative scenario. The mean concentration of EPA plus DHA of specific species was applied to match the concentration of DLCs in the pooled sample of the species for the calculation of mortality. According to the explanation given in the FAO/WHO publication[18], the value of X equaled 2 in all FAO/WHO equations in our assessment.

The results calculated by Equations (5) and (6) showed that the net benefits from the alternative scenario of all studied species were more than the net risks when mortality and child IQ gain were chosen as the common metrics for general population and for women of childbearing age, respectively (Table 3). Therefore, the benefit risk assessment of all studied species could be stopped at this level according to the BRAFO-tiered approach, and the alternative scenario of all studied species could be recommended over the reference scenario for general population and for women of childbearing age.

DISCUSSION

The net health effects caused by consumption of the studied species were calculated deterministically and the Monte Carlo simulation was dispensable when the FAO/WHO approach was applied alone for benefit risk assessment[18]. The deterministic computation might not have been performed if a clear conclusion was drawn before tier 3 according to the BRAFO-tiered approach, which indicated that the potential assessment process of the BRAFO-tiered approach would be simpler. Furthermore, this approach includes probabilistic computation to resolve possible inconsistent deterministic computation results from different samples belonging to the same species. However, the deterministic computation methods recommended by the BRAFO-tiered approach (e.g., QALY) required some basic information on the target population[16], which was unavailable in our study. Therefore, it would be suitable that we integrate the BRAFO-tiered and the FAO/WHO assessment approaches according to our data. We found neither the application of the BRAFO-tiered approach in terms of consumption of Western Pacific species nor the combined application of the BRAFO-tiered approach and the FAO/WHO deterministic approach in the literature before our study.

There would be optimal consumption of specific species for prevention of death and for child IQ gain because intake of EPA plus DHA has the respective maximum positive effect on death prevention and on child IQ gain[18]. The determination of the optimal consumption (g/week) of specific species for prevention of death would follow two steps: firstly, it would be determined if the net prevented number of deaths increases with the increment of consumption of the species according to Equation (5). If it does not, then the optimal consumption of the species would be zero; if it does, then the value (i.e., 'potential optimal consumption'), by which the mean of EPA plus DHA concentration multiplied equals 1750 (i.e., 250×7), would be calculated. Secondly, it would be determined if the 'potential optimal consumption' results in a DLCs exposure exceeding the PTMI. If it does not, then the optimal consumption of the species would be its 'potential optimal consumption'; if it does, then the optimal consumption of the species would be the value, under which the species consumption would not result in a DLCs exposure exceeding the PTMI. Similarly, the optimal maternal consumption of specific species for child IQ gain could also be determined by the aforementioned steps. Although the BRAFO-tiered approach does not refer to calculation of optimal consumptions, we still list the relevant calculated results (Table 4), because we considered that the optimal consumption would be a crucial reference value for general population and for women of childbearing age during consumption of specific species.

The concentration of DLCs in our studied species appeared to be generally low, at least compared with that in the species from the Pearl River Delta, China (0.596-4.458 pg TEQ/g in 10 marine species and 0.481-9.050 pg TEQ/g in 10 freshwater species)[25]. However, the species with relatively high DLCs concentrations in our study deserve concern, because an additional alternative scenario of these species would result in a significant over-PTMI exposure of DLCs in adult population with high DLCs exposure (P 97.5[23]), for example, the species *Auxis thazard*. Even though the assessment results indicated that the alternative scenario of all studied species could be recommended over the reference scenario (Table 3) and the alternative scenario of species with relatively high DLCs concentrations would displace other foods with higher DLCs concentrations, we still

Table 3. The Change of Mortality (deaths/million people) and IQ Point from Reference Scenario to Alternative Scenario

Scientific Name	Change of Mortality			Change of IQ Point					
	Prevented Deaths	Caused Deaths	Net Prevented Deaths	IQ Point Gain		IQ Point Loss		Net IQ Gain	
				x	*s*	*x*	*s*	*x*	*s*
Trichiurus lepturus	26,878	35	26,843	4.5	0.4	0.1	0.0	4.5	0.4
Larimichthys polyactis	34,532	71	34,461	5.5	0.5	0.0	0.0	5.4	0.5
Collichthys lucidus	8251	5	8246	1.4	0.3	0.0	0.0	1.4	0.3
Pampus chinensis	21,402	176	21,226	3.6	0.7	0.1	0.0	3.5	0.7
Muraenesox bagio	38,060	171	37,889	5.4	0.6	0.1	0.0	5.3	0.6
Conger myriaster	39,816	351	39,465	5.7	0.1	0.1	0.0	5.6	0.1
Sebastiscus marmoratus	20,428	34	20,394	3.4	0.8	0.1	0.0	3.3	0.8
Thamnaconus modestus	6241	5	6236	1.1	0.3	0.1	0.0	1.0	0.3
Scomber japonicus	39,816	252	39,564	5.8	0.0	0.1	0.0	5.7	0.0
Scomberomorus niphonius	23,703	103	23,600	4.0	0.7	0.1	0.0	3.9	0.7
Ilisha elongata	33,358	52	33,306	5.6	0.2	0.1	0.0	5.4	0.2
Miichthys miiuy	20,643	48	20,595	3.5	0.5	0.1	0.0	3.4	0.5
Sparus macrocephlus	30,887	247	30,640	5.0	0.8	0.1	0.0	4.9	0.8
Harpadon nehereus	8630	16	8614	1.5	0.2	0.0	0.0	1.4	0.2
Raja porosa	5625	85	5540	0.9	0.3	0.1	0.0	0.8	0.3
Mugil cephalus	12,117	227	11,889	2.0	2.1	0.0	0.0	2.0	2.1
Lateolabrax maculatus	39,067	14	39,053	5.5	0.5	0.1	0.0	5.4	0.5
Hexagrammos otakii	17,282	108	17,174	2.9	0.2	0.1	0.0	2.8	0.2
Oplegnathus fasciatus	21,376	172	21,204	3.6	0.2	0.1	0.0	3.5	0.1
Auxis thazard	39,816	1250	38,566	5.8	0.0	0.4	0.0	5.4	0.0

considered that the reference scenario (i.e., no intake) of these species (e.g., *Auxis thazard*) rather than the alternative scenario could be recommended to population exposed to high DLCs for the reason of cautiousness. After all, there was a lack of research on the type of probable displaced foods and on DLCs concentrations in these foods, and many alternative species with lower DLCs concentrations and more beneficial assessment results are available. *Auxis thazard* also has the highest MeHg concentration among our studied species; however, an additional alternative scenario of this species would not result in a MeHg exposure exceeding the PTWI in Chinese population, because the MeHg exposure was less than 10% of the PTWI in all studied Chinese population[4] and the MeHg intake via the alternative scenario of this species provided only approximately 25% of the PTWI (Table 2).

The consumption of oily fish was recommended to increase the intake of EPA and DHA[26-27]. However, the results of our study showed that health risk would also increase with the increment of oily fish consumption. Once again, this indicated that the consumption of *Auxis thazard*, a species with high concentrations of both n-3 LCPUFAs and studied contaminants, needs caution. We considered that the consumption of oily fish with relatively low concentrations of contaminants rather than all species of oily fish could be recommended.

The additive beneficial effects from dietary alpha linolenic acid (ALA) would draw more attention because it is a precursor for the endogenous synthesis of n-3 LCPUFAs and provides over 10% of the total fatty acids in rapeseed oil, the culinary oil with the largest average consumption in China. Epidemiological data showed that an increased intake of ALA could contribute to the reduction of CHD risk, especially in the population with low fish consumption, which indicates that the

Table 4. The Weekly Optimal Consumption (g) for Death Prevention and Maximum Prevented Deaths (deaths/million people)/DLCs Exposure (pg/kg bw/month) via Weekly Optimal Consumption*

Scientific Name	Weekly Optimal Consumption for Death Prevention	Maximum Prevented Deaths	DLCs Exposure
Trichiurus lepturus	296.3	39 764	1.5
Larimichthys polyactis	230.6	39 734	2.5
Collichthys lucidus	965.1	39 790	0.8
Pampus chinensis	372.1	39 489	9.8
Muraenesox bagio	209.2	39 637	5.4
Conger myriaster	195.8	39 472	10.3
Sebastiscus marmoratus	389.8	39 750	2.0
Thamnaconus modestus	1275.9	39 784	1.0
Scomber japonicus	139.8	39 640	5.3
Scomberomorus niphonius	336.0	39 644	5.2
Ilisha elongata	238.7	39 754	1.9
Miichthys miiuy	385.8	39 723	2.8
Sparus macrocephalus	257.8	39 498	9.5
Harpadon nehereus	922.7	39 744	2.2
Raja porosa	1415.7	39 212	18.1
Mugil cephalus	657.2	39 069	22.4
Lateolabrax maculatus	203.8	39 802	0.4
Hexagrammos otakii	460.8	39 567	7.5
Oplegnathus fasciatus	372.5	39 496	9.6
Auxis thazard	71.2	39 371	13.3

Note. *The data on the optimal maternal consumption for child IQ gain could be obtained from a previously published study[20].

dietary ALA could exert direct and/or indirect cardiovascular beneficial effect[28-29]. Furthermore, the endogenous conversion of ALA to n-3 LCPUFAs would be relatively more efficient in some specific populations, such as women of childbearing age[30-31] and vegetarians/vegans[32]. The conversion capability of dietary ALA to plasma DHA in neonate would be negligible[33], which indicates that breast milk would be the main source of DHA in exclusively breastfed neonate; on the other hand, dietary DHA of vegetarians/vegans is more likely to be deficient. Therefore, such efficient conversion in these populations would be a crucial compensation to meet their physiological demands. Based on the aforementioned description, we consider that the methodologies on benefit risk assessment would refer to n-3 LCPUFAs derived from endogenous synthesis, especially in some specific populations, to a greater extent.

The n-3 DPA is an intermediate product in the conversion of ALA to DHA, of which the content in most studied species would not be negligible[20]. Its beneficial effects have been reported based on animal studies[34]. Therefore, we listed n-3 DPA intake amounts via the alternative scenario (Table 2). However, the current benefit risk assessment could not refer to n-3 DPA, because the dose-response relationship between the intake of n-3 DPA and its beneficial effects in humans is still unavailable. The current benefit risk assessment could also not refer to some contaminants (e.g., polybrominated diphenyl ethers) and nutrients (e.g., minerals) in studied species for the same reason.

As mentioned above, n-3 LCPUFAs could actively affect the immune system[3]. On the other hand, the potential immunotoxicity of MeHg[35] and the DLCs-induced immunosuppressive effect on mouse B cell[36] were also reported. Moreover, some ingredients in marine species such as parvalbumin would be allergenic[37]. Therefore, a benefit risk assessment methodology that includes immunological end points deserves to be developed.

The Zhoushan Archipelago was chosen as the sampling location because it is a crucial fishing ground in China and provides aquatic foods, particularly marine fish, to the whole country, which indicates that our study results could be applicable to a large-scale population.

Our benefit risk assessment for child IQ gain does not need to be extended to tier 4 of the BRAFO-tiered methodology. Moreover, there was only pooled sample of each species for analysis of DLCs concentration in our study, which indicates that the net effect of death prevention could not be assessed in tier 4 of the BRAFO-tiered methodology because the distributional parameters for probabilistic computation of population mortality were unavailable. Analysis of DLCs concentration in individual sample was not feasible because it was a highly time-consuming process.

CONCLUSION

The results of the current study based on the BRAFO-tiered approach showed that the benefit of the alternative scenario (200 g/week) of all studied species outweighed its risk to population with an average DLCs exposure at tier 1, and the net benefits were quantitatively more than the net risks when mortality and child IQ gain were chosen as the common metrics for general population and for women of childbearing age at tier 3. Our results indicated that the alternative scenario of all studied species could be recommended to both these population groups with an average DLCs exposure, while the reference scenario (no intake) of species with relatively high DLCs concentration (e.g., *Auxis thazard*) could be recommended to population exposed to high DLCs for the reason of cautiousness.

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