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Biogenic amines in raw and processed seafood

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The presence of biogenic amines (BAs) in raw and processed seafood, associated with either time/temperature conditions or food technologies is discussed in the present paper from a safety and prevention point of view. In particular, storage temperature, handling practices, presence of microbial populations with decarboxylase activity and availability of free amino acids are considered the most important factors affecting the production of BAs in raw seafood. On the other hand, some food technological treatments such as salting, ripening, fermentation, or marination can increase the levels of BAs in processed seafood. The consumption of high amount of BAs, above all histamine, can result in food borne poisoning which is a worldwide problem. The European Regulation established as maximum limits for histamine, in fishery products from fish species associated with high histidine amounts, values ranging from 100 to 200 mg/kg, while for products which have undergone enzyme maturation treatment in brine, the aforementioned limits rise to 200 and 400 mg/kg. Preventive measures and emerging methods aiming at controlling the production of BAs are also reported for potential application in seafood industries.

Keywords: fish, histamine, bacteria, raw and processed seafood

INTRODUCTION

Seafood may harbor a number of biological, chemical, and physical hazards, the most prevalent of which are biogenic amines (BAs) and biotoxins (chemical), pathogenic bacteria and viruses (biological), and metal inclusion (physical). BAs are low molecular weight organic bases with biological activity that are formed in foods by microbial decarboxylation of the corresponding amino acids or by transamination of aldehydes and ketones by amino acid transaminases (Zhai et al., 2012). The most important BAs, histamine, tyramine, tryptamine, putrescine, and cadaverine, are formed from free amino acids namely histidine, tyrosine, tryptophane, ornithine and lysine, respectively. Spermidine and spermine arise from putrescine (Zarei et al., 2011). Putrescine, cadaverine, spermidine, and spermine have an aliphatic structure; histamine, and tryptamine have a heterocyclic structure and tyramine and phenylethylamine have an aromatic structure (Mohamed et al., 2009). The free amino acids either occur as such in foods or may be liberated through proteolysis. In addition to the availability of precursors (amino acids), BAs accumulation in foods requires the presence of microorganisms with amino acid decarboxylases and favorable conditions for their growth and decarboxylation activity (Zarei et al., 2011). Storage temperature is the most important factor contributing to BAs formation (Chong et al., 2011). Other parameters (i.e., pH, water activity, NaCl concentration, additives) may influence the variation of microbiota composition and lead to the differences in BAs content (Suzzi and Gardini, 2003). In addition, modified atmosphere packaging and vacuum packaging represent popular preservation methods which may inhibit the growth and increase the lag phase of microorganisms with amino acid decarboxylase activity (Chong et al., 2011).

The toxicological level of BAs is very difficult to establish because it depends on individual characteristics and the presence of other amines. However, a maximum total BAs level of 750–900 mg/kg has been proposed (Ladero et al., 2010).

The microbiological complexity of seafood is linked to the specific as well as non-specific microbial contaminants originating from the natural environment or being acquired during processing. The wide range of environmental habitats (freshwater to saltwater, tropical waters to arctic waters, pelagic swimmers to bottom dwellers, and degree of pollution) and the variety of processing practices (iced fish products to canned products) are all important factors in determining the initial contamination of fish and fish products (Gram and Huss, 1996). The types of bacteria that are associated with histamine production are commonly present in the saltwater environment. They naturally exist on the gills, on external surfaces, and in the gut of live, saltwater fish, with no harm to the fish. Upon death, the defense mechanisms of the fish no longer inhibit bacterial growth in the muscle tissue, and histamine-forming bacteria may start to grow, resulting in the production of BAs [Food and Drug Administration (FDA), 2011]. Evisceration and removal of the gills may reduce, but not eliminate, the number of histamine-forming bacteria. Packing of the visceral cavity with ice may aid in chilling large fish in which internal muscle temperatures are not easily reduced. However, when done improperly, these steps may accelerate the process of histamine development in the edible portions of the fish by spreading the bacteria from the visceral cavity to the flesh of the fish. With some harvesting practices, such as long-lining and gill-netting, death may occur many hours before the fish is removed from the water. Under the worst conditions, histamine formation can already be under way before the fish is brought onboard the vessel. This condition can be further aggravated with certain tuna species that generate heat, resulting in internal temperatures that may exceed environmental temperatures and increasing the

likelihood of conditions favorable to growth of enzyme-forming bacteria (FDA, 2011).

Some technological processes such as salting, ripening, fermentation or marination can increase the possibility of formation of BAs. A low pH (4.0–5.5), which can be achieved in salted anchovies, for instance, is favorable for enhanced amino acid decarboxylase activity (Pons-Sánchez-Cascado et al., 2005a). Moreover, important proteolysis is observed during ripening of salted anchovies, resulting in the liberation of peptides and free amino acids including histidine (Hernández-Herrero et al., 2002). The association of salted fish with histamine formation is probably due to the presence of halophilic or halotolerant microorganisms. For instance, Hernández-Herrero et al. (1999) reported that *Staphylococcus epidermidis* and *Staphylococcus capitis*, isolated from salted anchovies, showed a powerful histamine-forming activity, producing 1000 and 400 μg/ml, respectively. They assumed that the presence of these bacteria could be the result of contamination of fish during capture and subsequent unhygienic handling. BAs can also be produced throughout the manufacturing process, as well as during storage of the end product if improper holding temperatures are employed (Periago et al., 2003; Yongsawatdigul et al., 2004).

BACTERIA IN FISH

The microorganisms of fish intended for human consumption depend on the environmental conditions of its natural habitat. In particular, the microflora of fish from temperate water consists primarily psychrotrophic Gram-negative bacteria belonging to the genera *Pseudomonas, Moraxella, Acinetobacter, Shewanella*, and *Flavobacterium*. Members of the *Vibrionaceae* (*Vibrio* and *Photobacterium*) and the *Aeromonadaceae* (*Aeromonas* spp.) families are also common aquatic bacteria and typical of the fish flora [Food and Agriculture Organization (FAO), 1995]. Although Gram-negative bacteria are the predominant microorganisms in fish, Gram-positive bacteria such as *Bacillus, Micrococcus, Clostridium, Lactobacillus*, and coryneforms can also be found at various levels. *Aeromonas* spp. are typical of freshwater fish, whereas a number of bacterial genera such as *Vibrio*, *Photobacterium*, and *Shewanella* require sodium for growth and are, thus, typical of marine waters (Gram et al., 1990). In polluted waters, high numbers of *Enterobacteriaceae* may be found. In clean temperate waters, these organisms disappear rapidly, but it has been shown that *Escherichia coli* and *Salmonella* can survive for very long periods in tropical waters, and that once introduced, they may become indigenous to the environment (Fujioka et al., 1988).

The composition of fish microbiota changes quite dramatically during spoilage. *Shewanella putrefaciens* and *Pseudomonas aeruginosa* have been identified as the prominent spoilage bacteria of fresh fish (Gram and Huss, 1996). At ambient temperature (25°C), the microbiota at the point of spoilage is dominated by mesophilic *Vibrionaceae* and, particularly if the fish is caught in polluted waters, *Enterobacteriaceae*. Some *Pseudomonas* spp. are the specific spoilers of iced stored tropical freshwater fish and are also spoilers of marine tropical fish stored in ice (Gram and Huss, 1996). Many different bacterial species of the *Enterobacteriaceae* family are known to possess histidine decarboxylase activity and have the ability to produce histamine, including the species *Morganella morganii*, *Klebsiella pneumoniae*, *Hafnia alvei*, *Proteus vulgaris*, *Proteus mirabilis*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Serratia fonticola*, *Serratia liquefaciens*, *Raoultella* (formerly *Klebsiella*) *planticola*, *Raoultella ornithinolytica*, *Providencia stuartii*, and *Citrobacter freundii* (Kim et al., 2003). In addition to the enteric bacteria, *Clostridium* spp., *Vibrio alginolyticus*, *Acinetobacter lowffi*, *Plesiomonas shigelloides*, *Pseudomonas putida*, *Pseudomonas fluorescens*, *Aeromonas* spp., and *Photobacterium* spp. have also been reported as histamine formers (Chen et al., 2010). Emborg et al. (2006) identified *Morganella psychrotolerans*, a strong histamine-former, as a novel psychrotolerant bacterium, whereas the study of Kanki et al. (2004) revealed that these low temperature-adapted bacteria could play a role in scombroid poisoning.

BIOGENIC AMINES PRODUCTION IN RAW SEAFOOD

Histamine levels in freshly caught fish are generally low, usually below 0.1 mg/100 g (Auerswald et al., 2006). At any time, exposure of certain fish to elevated temperatures after the catch and before consumption can cause formation of histamine from histidine by bacterial histidine decarboxylases. While most studies agree that histamine formation is negligible in fish stored at 0°C or below, data concerning storage conditions at higher temperatures are variable and do not allow for the establishment of standard procedures for avoiding potential negative effects of transport/storage conditions on fish safety (Rossano et al., 2006). However, fish is more likely to form BAs when decomposition occurs at harvest or in the first stages of handling on the fishing vessels, rather than later in the distribution chain (Staruszkiewicz et al., 2004).

The term "scombroid" is derived from the name of the family *Scombridae* which includes the fish species that were first implicated in histamine intoxication (i.e., tuna and mackerel). These species of fish share in common high levels of free histidine in their muscle tissues. It is known that other non-scombroid fish species are also implicated in scombroid poisoning, such as mahi-mahi (*Coryphaena* spp.), sardines (*Sardinella* spp.), pilchards (*Sardina pilchardus*), anchovies (*Engraulis* spp.), herring (*Clupea* spp.), marlin (*Makaira* spp.), bluefish (*Pomatomus* spp.), Western Australian salmon (*Arripis truttaceus*), sockeye salmon (*Oncorhynchus nerka*), amberjack (*Seriola* spp.), Cape yellowtail (*Seriola lalandii*), and swordfish (*Xiphias gladius*). With the exception of salmon and swordfish, most of these fish species are rich in free histidine (Hungerford, 2010). However, it has been found that histamine poisoning may not be caused to all the people consuming contaminated fish. Given that histamine-forming bacteria may be diversely distributed in fish, the diffusion of produced histamine may also vary widely in different parts of the animal. For instance, while 50 mg/kg of histamine may be found in one fish section, its level may exceed 500 mg/kg in another (FDA, 2011). Thus, even if the same histamine-containing fish is ingested, some consumers may be poisoned and some may not (Tao et al., 2002, 2009).

Histamine is produced in raw fish from the action of bacterial histidine decarboxylase following temperature/time abuse. Production of histamine is greater, however, at high abusive temperatures (21.1°C or higher) than at moderate abusive temperatures (7.2°C), while its generation is particularly rapid at temperatures near 32.2°C (FDA, 2011). According to European Regulation fresh fishery products, thawed unprocessed fishery products, and

cooked and chilled products from crustaceans and mollusks must be maintained at a temperature approaching that of melting ice (European Commission, 2004). Rapid chilling of scombrotoxin-forming fish immediately after death is the most important element in any strategy for preventing the formation of histamine, especially for fish that is exposed to warm waters or air, and for tunas which generate heat in their tissues. Failure to chill onboard may permit bacteria and enzymes, including those that form histamine, to increase to high levels (FDA, 2011). Even if ice storage is recommended, temperature/time abuse conditions often occur in the fish merchandising chain. Delays in removing fish from the water after capture, such as those captured by a longline, may significantly limit the amount of time left for chilling and may allow some fish to heat up. Moreover, mishandling coupled with high temperature abuse are likely when handling fish and may significantly enhance histamine formation. The amount of post-harvest time at elevated temperatures (after proper chilling onboard the harvest vessel) to which a fish can be exposed (e.g., during processing, storage, and distribution) without adverse effects depends primarily on whether the fish was previously frozen (e.g., in the harvest vessel) or heat-processed sufficiently to destroy histamine-forming bacteria (FDA, 2011). Rossano et al. (2006) studied the influence of storage temperature and time of freezing on histamine formation in anchovies, showing the ability of freezing to inhibit or slow down its formation.

Many scientists have studied the effects of storage temperatures on histamine formation in fish and their results have been very often ambiguous. This can be explained by the differences in the composition and the level of microorganisms in the fish. Histamine producing bacterial species and strains vary considerably in amounts of histamine formation, and the type of spoilage bacteria present depends on the aquatic environment. It has been reported that *M. morganii*, *K. pneumoniae*, and *P. vulgaris* are prolific histamine formers, producing >1000 mg/kg in the culture broth (López-Sabater et al., 1996; Rawles et al., 1996; Kim et al., 2001). These species have rarely been detected in fresh fish, but have mostly been isolated from fish spoiled under controlled storage conditions, above 20°C (Ababouch et al., 1991; Kim et al., 2001). Bacteria occurring naturally in marine environments such as *Photobacterium* spp., *Pseudomonas* spp., *Vibrio alginolyticus*, and *Aeromonas* spp. have indeed been frequently isolated from fish stored at refrigeration temperature for extended periods (Middlebrooks et al., 1988; Morli et al., 1988). However they are weak histamine formers, producing <500 mg/kg in the culture broth (Frank et al., 1985). Then, in raw fish histamine content is linked to the type of histamine-forming bacteria, the type of seafood, and temperature/time storage conditions (**Table 1**). Typically, boats fish overnight in a trip of up to 12 h. Storage is at ambient temperature until unloaded at the processing plant, with the first-caught fish being already stored for up to 10 h. Such a long period may cause histamine-producers to undergo nine doublings, an increase of 1000 times (three log scales) over the assumed initial level of 10/g or cm^2, reaching a level of 10000/cm^2 at fish surfaces or 10000/g in the gut (FAO, 2004).

In addition to their toxicological implications, BAs are related to fish spoilage, since they accumulate as a result of the proteolytic and amino acid decarboxylase activity of microorganisms

Table 1 | Histamine content in fresh fish stored at abused temperature/time conditions.

Fish	Temperature/time	Histamine (mg/kg)	Reference
Pacific mackerel	25°C for 48 h	2830.0	Kim et al. (2001)
Yellowfin tuna	22°C for 5 d	4533.0	Du et al. (2002)
Albacore tuna	25°C for 6 d	671.0	Kim et al. (2002a)
Mackerel	25°C for 24 h (inoculated with *Morganella morganii*)	4610.0	Kim et al. (2002b)
Albacore		3430.0	
Mahi-mahi		3340.0	
Salmon		255.0	
Skipjack tuna	21°C for 48 h	1533.0	Rossi et al. (2002)
Mackerel	32.2°C for 9 h	28.0	Shakila et al. (2003)
	32.2°C for 12 h	50.0	
	32.2°C for 16 h	100.0	
Mahi-mahi	26°C for 12 h	50.0	Staruszkiewicz et al. (2004)
Skipjack tuna	25°C for 10 h	10.0	
Yellowfin tuna	25°C for 12 h	10.0	
Yellowfin tuna	20°C for 24 h	111.4	Guizani et al. (2005)
Sailfish	25°C for 24 h	2240.0	Tsai et al. (2005a)
Milkfish		3990.0	
Anchovy	25°C for 24 h	1465.0	Visciano et al. (2007)
Pilchard		1106.0	
Mackerel	25°C for 24 h	2123.9	Kim et al. (2009)
Saury		1776.7	
Spanish mackerel		189.9	
Amberjack		36.6	
Tuna fish	25°C for 48 h (inoculated with *Morganella morganii*)	2000.0–4000.0	Tao et al. (2009)
	25°C for 48 h (inoculated with *Photobacterium phosphoreum*)	1500.0–1800.0	

(**Table 2**). The use of more than a single BA (i.e., a BA index that consists of a combination of BAs) can be used as a quality indicator for fish freshness. Some examples are the sum of cadaverine and putrescine (Stede and Stockemer, 1981), the index of Mietz and Karmas (1981), which considers the increases in putrescine, cadaverine and histamine levels along with the corresponding decreases in spermidine and spermine, as well as the index described by Veciana-Nogués et al. (1997a) for tuna, which includes putrescine, cadaverine, histamine, and tyramine. In their study, Baixas-Nogueras et al. (2005) used these indexes for the freshness evaluation of iced Mediterranean hake (*Merluccius merluccius*) in the chilling conditions as applied in the merchandising chain. Putrescine and cadaverine were the main amines accumulated, whereas histamine and tyramine were less abundant. Cadaverine was the amine best correlated with *S. putrefaciens*, the specific spoilage organism, while putrescine showed the most satisfactory correlation with the genus *Pseudomonas*. According to the

obtained results, the authors proposed a BAs index limit of acceptability in a range of 15–20 μg/g. The study of Veciana-Nogués et al. (1997a), indeed, considered BAs as hygienic quality indicators in tuna (*Thunnus thynnus*), a fish belonging to the *Scombridae* family and therefore, with high levels of free histidine in its muscle. So, the value of 50 μg/g for the sum of histamine, tyramine, putrescine, and cadaverine, which was not exceeded in samples stored at 0°C before organoleptic rejection, was proposed as a guiding limit value for tuna acceptance.

BIOGENIC AMINES IN PROCESSED SEAFOOD

BAs formation is possible during processes such as brining, salting, smoking, drying, fermenting, and pickling until the product is fully shelf-stable (**Table 3**). Refrigeration can be used to inhibit histamine formation during these processes (FDA, 2011). Samples of fermented fish products (fish sauce, fish paste, and shrimp paste) were analyzed for histamine content (Tsai et al., 2006), which was 394, 263, and 382 mg/kg, respectively. Three fish sauces, two fish pastes, and two shrimp paste products contained greater than 500 mg/kg of histamine. Moreover 7.4% of the tested samples contained >1000 mg/kg. The average content of various BAs in tested samples was less than 90 mg/kg. The fish paste Rihaakuru, which is an important condiment in the Maldives, could contain high concentrations of BAs, due to raw tuna, from which the product is made from, being subjected to temperature abuse. Twenty-eight samples of Rihaakuru (Naila et al., 2011), were analyzed for some BAs; in particular, histamine was detected at the highest concentration (5487 mg/kg). Tryptamine was not detected in most of the samples (only three samples contained <5 mg/kg) and phenylethylamine only occurred at low levels (<25 mg/kg). The authors supposed that the histamine found in Rihaakuru samples was most likely to have originated from Gram-negative bacteria growing in the fish before processing or within the fish during the early steps of manufacture. There are other processed seafood which have been investigated for BAs content. In southern China, three fish products are widely consumed: salted and fermented fish, canned fish, and packaged fish. Zhai et al. (2012) examined 49 fish products from the China market. The maximum total BAs content of lightly cured horse mackerel was 484.42 mg/kg compared to 167.86 mg/kg or less for the other salted and fermented fish products. In the Spanish mackerel sample, histamine was detected within the range of 15.74–28.70 mg/kg, whereas the maximum histamine level was 26.95 mg/kg in canned anchovies, 22.38 mg/kg in canned sardines and less than 10 mg/kg in all other canned samples tested (Zhai et al., 2012). Mah et al. (2002) found high levels of histamine (155–579 mg/kg) in fermented fish products made from anchovies, whereas Huang et al. (2010) reported large amounts of histamine in dried fish products (63.1–479.0 mg/kg).

Ripened, semi-preserved anchovies are prepared from fish of the *Engraulis encrasicholus* species, and are a common tradition in some Mediterranean countries. Pons-Sánchez-Cascado et al. (2005a) studied BAs in salt-ripened anchovies reporting that tyramine was the most abundant amine, reaching values up to 90 mg/kg, whereas histamine did not exceed 20 mg/kg. Then, the same authors analyzed samples of vinegar-marinated anchovies and reported higher values for tyramine than histamine (7.81 and 0.54 mg/kg, respectively) in 14 days of refrigerated storage (Pons-Sánchez-Cascado et al., 2005b).

The applicability of lactic acid bacteria (LAB) in fermenting whole fish has been demonstrated. The fermentation process for fish may fulfill the conditions required for abundant formation of BAs, i.e., availability of free amino acids, the presence of decarboxylase-positive microorganisms and conditions allowing bacterial growth, decarboxylase synthesis, and decarboxylase activity (Petäjä et al., 2000). Some fish sauce products, particularly those made from sardine and mackerel, often contain large quantities of histamine, about 1000 mg/l or greater (Tsai et al., 2006; Kuda and Miyawaki, 2010), as a result of the histidine decarboxylase of *Tetragenococcus* spp., a halophilic lactic acid bacterium. However, most studies (Thapa et al., 2006; Muñoz-Atienza et al., 2011) showed that in fermented fish products LAB produced no histamine or other BAs. Kuda et al. (2012) reported the possibility of regulation of histamine accumulation in salted and fermented fish products by the addition of halophilic LAB, like a starter culture, isolated from nukazuke (salted and fermented fish with rice bran). In a total of 200 isolates from nukazuke fish, 13 strains produced histamine in histidine containing broth (0.5%) at levels more than 200 μg/ml, whereas 130 isolates produced no histamine. Furthermore, 22 of the tested strains appeared to suppress histamine production (Kuda et al., 2012).

HISTAMINE FORMATION AND POISONING

Histamine poisoning occurs throughout the world and is perhaps the most common form of toxicity caused by the ingestion of fish (**Table 4**). However, reliable statistics about its incidence do not exist because poisoning incidents are often unreported due to mild symptoms, lack of adequate reporting systems, or misdiagnoses by medical personnel of histamine poisoning as a food allergy (FAO, 2004).

Many BAs have been found in fish, but only histamine, cadaverine, and putrescine have been identified as significant concerns with regard to fish safety and quality (Al Bulushi et al., 2009). Despite the widely accepted association between histamine and scombroid food poisoning, histamine alone appears to be insufficient to cause toxicity, and putrescine and cadaverine have been suggested to potentiate its toxic activity by inhibiting the intestinal histamine-metabolizing enzymes, diamine oxidase and histamine N-methyltranferase (Stratton et al., 1991). The onset of scombroid poisoning is typically from 10 min to 1 h following consumption of fish and can last from 12 h to a few days. The symptoms are variable and include peppery or metallic taste, oral numbness, headache, dizziness, palpitations, rapid and weak pulse, drop in blood pressure, difficulty in swallowing, and thirst. Also noteworthy are allergy-like symptoms such as hives, rash, flushing, and facial swelling (Hungerford, 2010). Symptoms involving the central nervous system such as anxiety are less frequently observed. Less specific symptoms such as nausea, vomiting, abdominal cramps, and diarrhea are also experienced (Gilbert et al., 1980). Serious cardiac and respiratory complications may be caused in individuals with preexisting conditions (Ascione et al., 1997). In a few rare cases hospitalization, including treatment for anaphylactic shock, has been required (Sanchez-Guerrero et al., 1997).

Table 2 | Levels (mean value, mg/kg) of BAs in raw seafood.

Fish	Temperature/ time	Cadaverine	Putrescine	Spermidine	Spermine	Tyramine	Histamine	Reference
Tuna	0°C	0.7	0.3	6.8	22.4	0.0	0.2	Veciana-Nogués et al. (1997b)
Herring	0°C/0 days	8.5	0.0	0.0	0.0	0.0	0.0	Özogul et al. (2002)
	0°C/16 days	237.2	39.7	4.5	3.4	4.2	271.4	
Rainbow trout	0°C/0 days	0.0	7.5	4.1	0.3	0.2	0.0	Chytiri et al. (2004)
	0°C/18 days	2.7	23.1	13.6	5.1	2.9	1.6	
Mediterranean Sea bass	0°C/0 days	0.0	0.0	8.8	14.4	0.0	0.0	Paleologos et al. (2004)
	0°C/16 days	6.5	3.1	0.0	0.0	4.3	0.0	
Sailfish	0°C	2.1	0.3	0.4	2.7	0.1	4.6	Tsai et al. (2004)
Indian anchovy	35°C/0 h	15.5	0.0	49.3	6.2	46.9	14.0	Yongsawatdigul et al. (2004)
	35°C/16 h	863.4	259.9	55.2	27.1	273.0	2007.0	
Mediterranean hake	0°C/0 d	0.8	1.7	3.5	4.6	0.6	0.1	Baixas-Nogueras et al. (2005)
	0°C/14 days	20.3	12.2	10.7	15.0	2.4	2.2	
Sardine	4°C/0 days	3.9	13.4	1.2	0.0	0.0	19.5	Özogul and Özogul (2006)
	4°C/15 days	100.4	114.0	7.6	2.9	16.3	203.0	
Alaska pollack	0°C	6.3	36.3	7.1	0.5	1.9	0.0	Kim et al. (2009)
Pacific cod		2.6	4.2	3.1	4.3	3.7	0.0	
Pacific herring		59.5	43.9	3.0	3.2	23.3	9.1	
Pacific mackerel		0.0	9.8	35.2	3.8	40.3	2.7	
Bandfish	0°C	9.9	15.0	1.8	4.4	0.7	0.6	Zhai et al. (2012)
Golden pompano		1.0	1.2	2.5	6.0	0.1	0.1	
Blue scad		54.3	42.5	2.8	1.9	29.6	20.0	
Mackerel		1.6	0.7	0.2	1.8	0.1	10.2	
Pacific saury		52.0	3.7	0.2	0.6	21.2	9.1	

Table 3 | Levels (mean value, mg/kg) of BAs in processed seafood.

Product	Cadaverine	Putrescine	Spermidine	Spermine	Tyramine	Histamine	Reference
Canned tuna	0.6	0.2	4.0	10.8	0.0	0.4	Veciana-Nogués et al. (1997b)
Anchovies in oil	38.3	7.6	2.3	7.9	21.6	12.6	Veciana-Nogués et al. (1997c)
Fish sauce	685.5	308.2	9.9	3.7	117.3	574.7	Yongsawatdigul et al. (2004)
Fish sauce	89.0	24.0	9.0	52.0	9.4	394.0	Tsai et al. (2006)
Fish paste	58.0	12.0	15.0	60.0	8.8	263.0	
Shrimp paste	80.0	40.0	36.0	43.0	3.7	382.0	
Dried milkfish	949.0	44.0	7.0	23.0	85.0	4097.0	Hsu et al. (2009)
Bullet mackerel	1.1	8.2	256.2	162.6	11.5	39.3	Huang et al. (2010)
Round scad	13.3	41.3	22.0	258.0	48.8	31.8	
Smooth-tailed trevally	145.0	63.3	0.0	11.5	59.2	210.7	
Pacific round herring	30.2	11.4	85.8	258.3	0.0	9.1	
Salted mackerel	2.0	0.0	5.5	2.0	6.0	0.9	Park et al. (2010)
Canned mackerel	7.8	2.3	4.3	1.8	4.7	1.4	
Canned tuna	1.7	1.8	3.0	4.4	3.2	1.4	
Canned salmon	1.2	0.2	1.0	4.7	1.1	0.0	
Fish paste	387.0	290.0	14.6	15.8	5.1	5080.0	Naila et al. (2011)
Salted escolar roe	17.2	21.8	51.3	40.7	24.8	6.2	Hwang et al. (2012)
Light cured horse mackerel	244.4	64.5	0.2	0.0	62.8	21.3	Zhai et al. (2012)
Canned bandfish	53.1	18.4	0.0	0.7	17.3	1.1	
Canned anchovy	23.9	2.8	2.0	1.1	3.0	19.8	
Salted ice fishes	5.8	51.1	47.7	51.8	0.4	0.1	

Table 4 | Outbreaks of scombroid poisoning: source, geographical location, period, and number of involved cases.

Source	Location	Period	No. cases	Reference
Canned tuna	USA	1973	254	Merson et al. (1974)
Mackerel, tuna, anchovies, sardines, marlin	Japan	1970-1980	4122	Taylor (1986)
Dried horse mackerel	Japan	1973	2656	Taylor (1986)
Tuna, mackerel	Italy	1979	250	Molinari et al. (1989)
Yellowtail	South Africa	1992	22	Müller et al. (1992)
Tuna (fresh/frozen, canned), mackerel	United Kingdom	1987-1996	243 (sporadic) 105 (general) 56 (family)	Scoging (1998)
Fish	USA	1993-1997	297	Olsen et al. (2000)
Yellowtail	South Africa	2004	19	Anonymous (2004)
Canned mackerel	Taiwan	2001	3	Tsai et al. (2005b)
Tuna	South Africa	2004	1	Auerswald et al. (2006)
Fish	USA	1998-2002	463	Lynch et al. (2006)
Swordfish	Taiwan	2004	43	Chang et al. (2008)
Dried milk fish	Taiwan	2006	3	Huang et al. (2010)
Fried fish cubes	Taiwan	2007	347	Chen et al. (2010)

According to the FDA guidelines (FDA, 2011), the toxicity and defect action levels of histamine, established for tuna, mahi-mahi, and related fish, are the 50 mg/100 g and 5 mg/100 g, respectively; the term "defect action level" refers to the level of histamine naturally or inevitably occurring in foods without, however, presenting a considerable hazard for humans. According to the EU Regulation No 2073/2005 nine samples should be taken from each batch of fish species of the following families: *Scombridae, Clupeidae, Engraulidae, Coryfenidae, Pomatomidae, Scombresosidae.* These samples must fulfill the following requirements:

Mean value of all samples must not exceed 10 mg/100 g;
Two samples may be >10 mg/100 but <20 mg/100 g;
No sample may exceed 20 mg/100 g.

However, fish belonging to these families that have undergone enzyme ripening in brine may have higher histamine levels, but not more than twice the above values.

ANALYTICAL METHODS FOR BAs DETECTION

The number and variety of methods developed for laboratory histamine testing of fish and fishery products is impressive. In contrast to many of the other more potent seafood toxins, the relatively high action levels established for histamine in fish allow for its detection by a variety of different approaches ranging from simple and inexpensive thin layer chromatography (TLC) procedures to resource-intensive and more powerful liquid chromatography-mass spectrometry (LC-MS) methods (Hungerford, 2010). Most of the histamine separation methods applied in fish use reversed-phase high performance liquid chromatography (HPLC) with detection schemes based on pre-column derivatization (Mietz and Karmas, 1978; Hui and Taylor, 1983; Malle et al., 1996) or post-column derivatization (Glória et al., 1999; Brillantes and Samosorn, 2001) to produce fluorescent products or strong chromophores, but direct UV detection of histamine imidazole ring has also been applied (Shakila et al., 2001; Cinquina et al., 2004b). Other popular separation-based methods include ion chromatography (Cinquina et al., 2004a), capillary electrophoresis (Zhang and Sun, 2004), paper electrophoresis (Sato et al., 2002, 2006), TLC (Bajc and Gacnik, 2009), and gas chromatography-mass spectrometry (Marks and Anderson, 2006). In addition, there is a need for methods well suited to high-speed screening. The most rapid method for detecting histamine is based on flow injection analysis (FIA) and is capable of screening 60 sample extracts/hour (Hungerford et al., 1990). Enzymatic methods are attractive for their selectivity and flow injection has been used in combination with enzyme electrodes for easy automation (Watanabe et al., 2007). Many other commercial test kits are available, based on selective antibodies (Lehane and Olley, 2000; Köse et al., 2009). Commercial test kits based on immunoassay methods for histamine analyses became popular because of their user friendliness and reduced time requirements compared to those of traditional analytical techniques. Recently many authors (Köse et al., 2011; Tahmouzi et al., 2011; Tao et al., 2011; Hungerford and Wu, 2012) report different methods for rapid determination of histamine in fish.

CONTROL MEASURES

The FDA has issued industry guidelines aiming at establishing procedures for the safe processing and importing of fish and fishery products based on the hazard analysis and critical control points (HACCP) approach (FDA, 2011). According to the most recent HACCP guidelines for the control of histamine production, a core temperature of 4.4°C or less should be achieved and maintained throughout handling, processing, and distribution of potentially hazardous fish. The primary goal of these guidelines is the growth inhibition of spoilage bacteria capable of producing histamine through proper handling and chilling of fish (FDA, 2011). In order to achieve this objective, all boats should ice fish immediately after landing aboard the vessel so that the temperature at sites of microbiological concern is reduced at levels capable of controlling the growth of histamine-producing bacteria. Moreover, an ice-plant

could be built and ice made available at reasonable cost. Other spaces could also be modified so that the boats could be capable of carrying up to 100 kg of ice (FAO, 2004). It must be highlighted, however, that the time required to lower the internal temperature of fish after capture depends on a number of factors, including: (i) the harvest method; (ii) the size of the fish; (iii) the chilling method. Once chilled, the scombrotoxin-forming fish should be maintained as close as possible to the freezing point (or held frozen) until it is consumed (FDA, 2011).

At the processing plant, fish is gilled and gutted, then stored in ice until packed for air transport to the consumer country. Histamine decarboxylase activity could lead to a 10-fold increase in histamine during processing, air freight and marketing. The preventive measures for this step include controlling refrigeration temperature in the plant or performing proper icing during storage of raw material, in-process product as well as finished product (FAO, 2004). During processing of fish (butchering, cleaning, brining, salting, smoking, drying, fermenting, pickling, mixing, stuffing, packing, labeling, and staging), it is recommended that it is not exposed to ambient temperatures above 4.4°C for more than 12 h cumulatively, if it has been previously frozen or heat-processed sufficiently to destroy histamine-forming bacteria, or for more than 4 h in the other case (FDA, 2011). Given the heat-stable nature of histamine, the intended use of the product is not likely to affect the significance of this hazard. Recontamination of seafood with enzyme-forming bacteria in conjunction with temperature abuse may also allow for histamine formation following cooking. Thus, a conscientious sanitation program during seafood processing is of vital importance in order for recontamination events to be avoided.

Many recent studies proposed a new approach based on the employment of microorganisms or substances (additives, spices, disinfectants) able to inhibit histamine-forming bacteria. Mah and Hwang (2009a) studied the effects of food additives on BAs-producing strains of *Bacillus licheniformis* isolated from Myeolchi-jeot, with the greatest inhibitory effect being observed for glycine. The same product (Myeolchi-jeot) was ripened with the addition of a starter culture of *Staphylococcus xylosus*, which was shown to be capable of degrading histamine and tyramine (Mah and Hwang, 2009b), while the use of spices, in particular garlic, also showed an inhibitory effect (Mah et al., 2009). The development of post-harvest treatments for reducing histamine-forming bacteria in fish upon harvest is an important intervention strategy to prevent histamine formation in fish and control scombroid poisoning. Phuvasate and Su (2010) investigated the efficacy of treatments with electrolyzed oxidizing (EO) water and EO ice, containing 100 ppm chlorine. According to these researchers, soaking of fish (salmon) in EO water reduced *Enterobacter aerogenes* and *Morganella morganii* by 1.3 and 2.2 log CFU/cm^2 respectively, while soaking yellowfin tuna in EO ice reduced the same microorganisms by 2.4 and 3.5 log CFU/cm^2, respectively. Moreover, emerging methods potentially applied as control measures include the addition of starter cultures that degrade histamine, the application of hydrostatic pressure, irradiation, and packaging (Naila et al., 2010).

CONCLUSION

Seafood is susceptible to contamination by BAs-producing microorganisms at different points of the food chain. High levels of BAs can be prevented through the application of good hygiene practices and proper temperatures during handling, delivery and storage. Although BAs formation is the result of bacterial growth, the presence of these undesirable compounds, especially histamine, is not always noticed by consumers. In fact, while a fish with obvious spoilage will most likely not be consumed, a fish with a good appearance and no detectable spoilage odors may be consumed even if it contains a high histamine level. Thus, the application of appropriate control measures is fundamental for assuring seafood safety and such a responsibility is shared among the seafood catchers, processors, distributors, retailers, and merchants.

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