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Review article

A review of biogenic amines in fermented foods: Occurrence and health effects

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ABSTRACT

Biogenic amines (BAs) are low-molecular decarboxylation products of amino acids formed during microbial fermentation. Several fermented foods may contain BAs such as histamine, tyramine, and/or phenylethylamine, at levels above documented toxic doses. Dietary exposure to foods containing high levels of BAs is associated with many adverse health effects, such as migraines, elevated blood pressure, and tachycardia. BA-mediated toxicity may occur at levels a hundred times below regulatory and suggested toxic doses, depending on an individual's sensitivity and factors such as alcohol consumption and certain medications. Although BAs occur in a wide variety of fermented foods, food safety and public health professionals are not well informed about the potential health risks and control strategies in these foods. In this review, we highlight the health risks and symptoms linked to BA exposures, the BA levels found in different fermented foods, regulatory and suggested toxic doses, and risk mitigation strategies to inform food industry and public health professionals' practice.

1. Introduction

Biogenic amines (BAs) are low-molecular weight organic bases that form during fermentative processes when microbial species decarboxylate amino acids, forming the corresponding amine and CO_2, or by amination, and transamination of ketones and aldehydes [1]. Small amounts of BAs in food do not normally cause adverse human health effects because they are associated with several biological functions and their presence is tolerated [2]. Additionally, intestinal amine oxidase enzymes rapidly metabolize and detoxify small amounts of BAs [2]. However, high BA concentrations can overwhelm the detoxification capacity of amine oxidases and cause minor allergic reactions and even serious health problems [1–3]. Several studies have reported elevated levels of BAs in various food categories including fish, fish products, and many fermented foods, such as meats, vegetables, dairy, and soy products [4,5]. BAs are not deactivated by thermal treatments that are often used to process and prepare food. The availability of free amino acids is usually the main factor driving BA production in foods; however, the quality of raw food ingredients and native microbial flora are also major factors [1]. Amino acid decarboxylase enzymes, responsible for BA formation, are widely present in spoilage and other food microorganisms, including those microbes involved in food fermentation [6]. Hence, several different methods can prevent BA formation, including better selection and control of microbial starter culture, using good quality food ingredients, maintaining strict sanitation, and observing proper food handling practices during the fermentation process. The common microbes that produce BAs through decarboxylation of amino acids include *Lactobacillus, Leuconostoc, Lactococcus, Enterobacter, Escherichia, Enterococcus,*

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Pediococcus, Pseudomonas, Streptococcus, Staphylococcus, Shigella, Salmonella, and *Bacillus* species [7,8]. *Lactobacillus* spp. are known to be mainly responsible for histamine, tyramine, and putrescine production in foods while *Enterobacteriaceae* and *Enterococcus* spp. are known to contribute to production of putrescine, cadaverine, and tyramine in foods [1]. Although using fresh and good quality ingredients can limit some types of spoilage bacteria, many of the bacterial genera listed above also drive natural fermentation and are normally present.

Dietary exposures to elevated levels of BAs through food can be toxic, depending on quantitative and qualitative factors associated with the food, individual susceptibility and health status [9]. High exposure to BAs is associated with several physiological symptoms, such as nausea, respiratory distress, headache, sweating, heart palpitations, and hyper- or hypotension [10]. Although histamine has been given much more attention due to its higher toxicity, several reports in the literature also indicate concerns regarding other BAs, such as tyramine, putrescine, phenylethylamine, and cadaverine [11].

Several regulatory agencies including Health Canada, the United States Food and Drug Administration (FDA), and the European Food Safety Authority (EFSA), have set action levels for histamines in fish and fish products [12]. However, there are no guidelines for other fermented food products or other BAs, such as tyramine and phenylethylamine. The goal of this review is to identify the health risks and symptoms linked to BA formation and describe the BA levels found in different categories of fermented foods. Moreover, the review will discuss the regulatory thresholds, identify risk mitigation strategies, and communicate best practice recommendations for the food industry and public health professionals. This review supported the development of fermented foods guidance by the Canadian national fermented foods working group, which is a sub-committee of Health Canada's Federal-Provincial-Territorial Food Safety Committee.

2. Results and discussion

2.1. Factors contributing to BA formation

BA can be naturally produced from normal metabolic activities in humans, animals, plants, and microorganisms [11]. The key requirements for excess BA formation include several factors, such as the availability of free amino acids, the presence of decarboxylase-positive non-starter microbiota, the composition, pH, ion strength, and water activity of the raw material, and conditions that favor bacterial growth during food processing and storage [13]. All these factors influence production of the required substrates, enzymes, and their activity levels, including the type and amount of BAs present in food [9]. BA formation in cells is, in effect, a defense mechanism bacteria use to combat stress or acidic environments [11]. It also helps to restore the pH by producing amines, and is a way of obtaining additional energy when needed [11].

In fermented foods, there is normally a massive growth of microorganisms, which may cause significant BA accumulation, especially in wild ferments without added starter culture [7,14]. BAs can be produced by both gram-positive and gram-negative bacteria. Lactic acid gram-positive bacteria in wild fermentations are mainly considered responsible for the production and accumulation of BAs in fermented foods [6,8,15].

BAs are thermostable; if they are already present in foods prior to pasteurization, cooking, etc., they will be not be destroyed [13]. Hence, to obtain food with low BA levels, it is important to select specific starter cultures that are deficient in BA accumulation pathways and are able to outgrow autochthonous microbiota under processing conditions [8]. Fermentation generally stimulates BA production; therefore, to limit BA accumulation, it is necessary to optimize processing conditions, such as quality of raw materials, temperatures favorable for starter culture growth, control microorganisms, and correct concentrations for additives e.g., sugar, salt, antimicrobial agents [13,14]. In one example linked to poor quality of raw materials, the formation of excess BAs in meat was linked to the preservation conditions, such as duration and temperature of freezing or thawing, and processing in the presence of bacteria with decarboxylase activity [9,16,17]. Another study found that the quality of raw materials affects the composition and levels of BAs produced in sausage during the ripening process [18]. In this study, lower microbial counts and BA index (the sum of histamine, tyramine, cadaverine, and putrescine) were observed in sausages when low amine containing raw material was used and hygienic quality maintained [18]. Even though the factors contributing to high levels of BA formation are well known, it can still be challenging to prevent BA accumulation since amino-biogenic ability is strain dependent and it can be difficult to modify fermentation conditions [8].

2.2. Mechanisms of BA formation in fermented foods

Biogenic amines in fermented foods are formed in the presence of free amino acids that are produced when the proteins in fermented foods are hydrolyzed by microbial-derived proteases [19]. These free amino acids act as substrates to microbial enzymes. The reactions leading to BA formation include decarboxylation of amine acids, which is the major route in fermented foods, or amination and transamination of ketone and aldehydes [19]. The decarboxylation occurs by the removal of the α-carboxyl group from the precursor amino acid. The amino acid precursors of the most common BAs are histidine (for histamine), tyrosine (for tyramine), phenylalanine (for phenylethylamine), tryptophan (for tryptamine), ornithine and agmatine (for putrescine), lysine (for cadaverine) [19,20]. Among these, only one-step decarboxylation of histidine, tyrosine, tryptophan, lysine and phenylalanine can produce the corresponding BA [19]. Putrescine is a diamine that can be produced either by decarboxylation of ornithine or by deamination of agmatine pathways [21]. Spermine and spermidine are polyamines that can be produced from putrescine by sequential addition of amino-propyl groups to putrescine [22].

2.3. Toxicological effects of BAs

Biogenic amines play important roles in many natural biological processes, including synaptic transmission, blood pressure and body temperature control, secretion of gastric acid, allergic response, and cell growth and differentiation [23]. However, exposure to high BA levels is associated with various adverse health effects, such as nausea, respiratory distress, hot flushing, sweating, heart palpitations, headache, bright red rash, burning sensations in the mouth, alterations in blood pressure, diarrhea, and hypertension [14,23]. The exact toxicity thresholds for BAs are difficult to determine because the toxic dose strongly depends on the effectiveness of the detoxification mechanisms, which may vary between individuals. Variation depends on individual sensitivity, alcohol consumption, and intake of drugs, which act as monoamine oxidase inhibitors or interact with the amine oxidase enzymatic pathways responsible for detoxifying excess BAs [8,24,25]. When the capacity of amine-metabolizing enzymes is over-saturated or when specific inhibitors disrupt metabolic activity, vasoactive BAs, such as histamine, tyramine, and phenylethylamine, may cause food intoxication [26]. Therefore, the focus should not only be on the concentration of one particular BA, but on the amount of food intake, the presence and levels of other amines in the food, exposure to BAs from other dietary components, as well as alcohol and certain medicine consumption [27].

Among all the BAs, histamines and tyramines are known to be the most toxic due to the severity of their associated symptoms. Histamines are responsible for "scombroid fish poisoning". Poisonings occur when fish species containing high levels of muscle histidine, such as tuna, sardines, anchovies, mackerel, and salmon, are temperature abused, allowing bacteria naturally present on the fish to multiply and convert muscle histidine to histamine [27,28]. The symptoms of scombroid poisoning develop after a few hours of exposure and are similar to allergic reactions, such as flushing of the face, neck, and upper arms, oral numbness and/or burning, headache, heart palpitations, asthma attacks, hives, gastrointestinal symptoms, and swallowing difficulties [8]. The histamine doses associated with allergic reactions may vary between individuals. Although scombroid fish poisoning can occur from fermented fish, fish sauces, and fish pastes, it is not associated with fermented fish specifically, but from consuming fish containing high histamine levels produced by spoilage activity from enteric gram-negative bacteria. For histamine, the current threshold levels are based on a limited number of available human studies, including both healthy and sensitive individuals. In healthy individuals, adverse effects are not expected with a histamine exposure level of 25–50 mg per person per meal. But in individuals with histamine intolerance, even a small amount of histamine exposure (5–10 mg) from food may cause severe adverse health effects [11,24]. Moreover, alcohol consumption can have a synergistic effect that amplifies histamine toxicity by inhibiting the detoxification activity of amine oxidases [29].

Tyramine intoxication is also known as "cheese reaction" or "cheese effect" because it was initially observed after consumption of cheese contaminated with high tyramine levels [8,28]. Symptoms occur within the first 2 h after consumption and include migraine, gastrointestinal symptoms, tachycardia, increased blood glucose, noradrenaline ejection, and hypertension [8,28]. For individuals prescribed monoamine oxidase inhibitors (MAOI), dietary exposures to tyramine is very important due to its toxicity and potential interaction with MAOI, which can raise blood pressure [30,31]. Currently there is inadequate information on tyramine to establish a toxic threshold in humans. However, based on limited published information in healthy individuals who were not taking any MAOI medicines, no adverse health effects were observed from up to 600 mg of tyramine per person per meal [11]. In comparison, for individuals who were taking third generation MAOI drugs, no adverse health effects were observed up to 50 mg of tyramine per person per meal, and for individuals taking classical MAOI drugs, a level of only 6 mg of tyramine per person per meal was considered safe; a level that would very easily be exceeded by consuming fermented foods [11].

Phenylethylamine, in the presence of tyramine, has been known to trigger food-induced migraine attacks and increase blood pressure [11]. A phenylethylamine dose of only 3 mg is linked with migraine headaches in sensitive individuals [27,32]. The doses of 100 mg/kg of histamine, 100–800 mg/kg of tyramine, and 30 mg/kg of phenylethylamine in food have been suggested to be toxic [27].

In 2011, according to an EFSA expert panel, the available information at the time was not adequate to determine a safety threshold for putrescine and cadaverine for acute adverse health effects in humans [11]. While putrescine and cadaverine do not cause significant symptoms individually, evidence suggests that their presence at elevated levels can enhance the toxic effects of histamine and tyramine by inhibiting their detoxification by enzymes. An Austrian study suggested tolerable cadaverine and putrescine levels in cheese, fermented sausages, fish, sauerkraut, and seasonings based on toxicological threshold levels in animals, occurrence of BAs in foods, and food consumption rates in Austria [33]. However, the study also acknowledged that the tolerable levels may be associated with some uncertainty due to limited data [33]. The study proposed maximum tolerable levels of 140–510 mg/kg for putrescine and 430–1540 mg/kg for cadaverine, depending on the type of fermented food [33]. Nevertheless, excess amounts of putrescine and cadaverine produced during spoilage of processed meats and seafood serve as the main indicators of spoiled food. They are responsible for unpalatable flavors, which prevents consumption of the contaminated foods [34].

Table 1
Summary of suggested and reported thresholds available for biogenic amines in foods.

	Suggested dose in food (mg/kg)	Toxic dose per meal in healthy individuals (mg)	Toxic dose per meal in sensitive and compromised individuals (mg)
Histamine	100	>50	5 to 10
Tyramine	100 to 800	>600	>6
β-phenylethylamine	30	None established	None established
Putrescine, cadaverine spermidine, tryptamine, spermine	None established	None established	None established
Reference	[24,27]	[11,32]	[11,24,27]

When subjected to heat, several BAs (spermidine, spermine, tyramine, putrescine, and cadaverine) can lead to the formation of secondary amines. This is critical for meat products such as sausages, which often contain high BA levels along with nitrate and nitrite additives, which can generate secondary amines, such as highly carcinogenic nitrosamines [9]. Although polyamine agmatine, spermine, and spermidine have many cellular functions, there is evidence of toxicity from excess levels in animal studies. Spermine and spermidine have been associated with blood pressure decreases, inhibition of blood clotting, respiratory symptoms, and neurotoxicity leading to renal insufficiency in experimental animals [35].

A review of the suggested toxicological reference values described for health concerns of BA in foods are summarized in Table 1.

2.4. Action levels and regulations

It is challenging to establish toxicological thresholds for BAs because the severity of toxic effects varies between individuals, depending on their sensitivity and the presence of other amines in foods. The toxicological threshold can range from a few mg/kg in sensitive individuals to several hundred mg/kg in a healthy person [14]. It has been reported that approximately 1000 mg/kg can be considered a risky level of total BA in food [1,36]. Several regulatory organizations such as Health Canada, US FDA, EFSA, Food and Agriculture Organization/World Health Organization (FAO/WHO), have set legal maximum limits for histamine levels in fish and fermented fish products to ensure safe human consumption. Even though dietary exposure to high BA level is associated with toxicological consequences, there are no specific regulations set by these organizations regarding BA contents in foods, except for histamine in fish and fish products.

Table 2 summarizes the regulatory thresholds for BAs in various countries and regulatory agencies. Health Canada regulates histamine levels in anchovies [12], fermented fish sauces, and pastes, while the US FDA has set a guidance level for histamine in fish [37]. European Commission, FAO/WHO and Codex have established limits for histamine in different fish and fish products [26,38,39]. Several other countries, including Australia, New Zealand, Turkey, Korea, Finland, Switzerland and the Slovak Republic have specific regulatory limits for histamine in fish and/or seafood [38–40]. Additionally, the Slovak Republic has set an upper limit for tyramine in cheese [39].

2.5. Occurrence of BAs in different fermented foods

The maximum values for BAs in five categories of fermented foods are shown in Table 3 for soybean, fish, meat, dairy, and vegetable foods. Based on the suggested quantitative risk values for histamine, tyramine, and phenylethylamine in food intended for human consumption, we identified reports of fermented foods that exceeded the suggested toxic doses of these biogenic amines. Such high levels of biogenic amines, specifically histamine or tyramine exceeding 100 mg/kg, and phenylethylamine exceeding 30 mg/kg [27], can potentially pose a health risk to individuals consuming these fermented foods.

2.5.1. Fermented soybean foods

Fermented soybean foods contain a large amount of dietary amino acid precursors of BAs and BA-producing microorganisms. *Enterobacteriaceae, Bacillus*, *Clostridium, Lactobacillus*, and *Pseudomonas* are some common microorganisms capable of producing BAs in fermented soy foods [42]. Some popular soybean foods produced by fermentation include soy sauces, natto, Japanese fermented soybean pastes (miso), Korean fermented soybean pastes (cheonggukjang, doenjang, gochujang), Chinese bean curd (sufu), Chinese

Table 2
Countries with thresholds established for biogenic amines.

Biogenic amine	Threshold	Country or Agency	Food product
Histamine	400 mg/kg	EFSA FAO/WHO	fermented fish sauces
	200 mg/kg	Canada	Anchovies, fermented fish sauces and pastes
	200 mg/kg	FAO/WHO Codex Alimentarius Australia New Zealand Turkey Korea Slovak Republic	fish and fish products
	100 mg/kg	Canada Finland Switzerland	fish and fish products
	200 mg/kg–400 mg/kg	EFSA	salted fish of Scombridae, Clupeidae, Engraulidae, Coryfenidae, Pomatomidae, Scombresosidae origin
	100 mg/kg–200 mg/kg	EFSA	fish of Scombridae, Clupeidae, Engraulidae, Coryfenidae, Pomatomidae, Scombresosidae origin
	50 mg/kg	USA	edible fish
Tyramine	200 mg/kg	Slovak Republic	Cheese

Table 3
Maximum biogenic amine content reported in fermented food categories.

	Maximum exposure levels of BAs (mg/kg) reported in the literature								Method of detection	References
	His[a]	Tyr[a, b]	Phe[a]	Trp	Put	Cad	Spd	Spm		
SOYBEAN BASED FOODS										
Soy sauce	**398.8**	**794.3**	**121.6**	73.34	1007.5	48.86	53.1	54.59	HPLC	[26,41]
Natto	**457**	**300.2**	**51.5**	301	43.1	42.0	478.1	80.1	HPLC	[26,42,43]
Miso	**221.0**	95.3	**42.0**	762	34.29	201	35.7	216	HPLC	[42]
Cheonggukjang	**755.4**	**2539**	**562.4**	236.4	476.3	268.2	79.1	182.7	HPLC	[26,41,44]
Doenjang	**2795**	**6616**	**8704**	2808	4292	3236	8804	9730	HPLC	[26]
Gochujang	59.0	**126.8**	24.8	36.6	36.4	18.1	14.5	14.8	HPLC	[26]
Sufu	**1187**	**1537**	**238.9**	769.9	2352	606.5	117.2	48.3	HPLC	[45–48]
Doubanjiang	ND	25.8	**185.6**	62.43	129.2	0.2	0.2	1.7	HPLC	[49]
Douchi	**808**	**529**	**736.6**	440	596	672.3	719	242	HPLC	[48,50]
Ssamjang	114.1	13.5	28.3	76.9	46.2	24.5	15.5	23.4	HPLC	[41]
Tempeh	ND	10.68	ND	15.6	3200	225	105.5	21.9	HPLC	[42,51]
FERMENTED FISH										
Fermented salted fish	**421.7**	62.6	9.2	44.4	84.7	142.5	25.8	2.9	HPLC	[52]
Fish sauce	**783.9**	**469**	7.7	270.6	276.6	606.3	56.2	19.4	HPLC	[53,54]
Ikan pekasam	73.9	**110**	**37.2**	29.7	249.4	211.2	7.4	9.5	HPLC	[55]
Fermented fish paste	**368.6**	**1002.9**	**152**	139.7	558.4	540.8	62.07	238.3	HPLC	[56,57]
FERMENTED MEAT										
Fermented sausage	**514.5**	**509.9**	25.2	49.8	505.3	689.8	10.2	36.7	HPLC	[58]
Marinated fermented beef	ND	**437.5**	NA	NA	139.5	582	ND	ND	IELC	[59]
Fermented pork (nham)	45.2	**385**	NA	NA	531.1	170.9	6.54	26.02	HPLC	[60]
Salami	**500.2**	**346.9**	**375.9**	297.1	818.5	215.9	99.7	151.9	HPLC	[61]
Dried sausage	**119**	**412**	**109**	33	307	409	17.5	43.7	HPLC	[62]
FERMENTED DAIRY										
Blue cheese	**140**	**1306**	**60**	170	258	120	30	20	HPLC	[63,64]
Mish cheese	**290**	**190**	**120**	220	200	220	40	20	HPLC	[64]
Feta cheese	84.6	**246**	4.94	5.74	193	82.8	ND	ND	HPLC	[65]
Cheddar cheese	29.4	44.5	2.3	NA	2.9	4.5	26.6	6.4	HPLC	[66]
Parmesan cheese	**148**	**103**	8.6	ND	6.1	12.7	30.7	0.3	HPLC	[66]
Hard cheese	**1025**	**561**	**44**	110	269	281	NA	NA	HPLC	[67]
Semi-hard cheese	**444**	**1029**	**219**	69	98	406	NA	NA	HPLC	[67]
Soft cheese	**176**	**393**	20	15	253	904	NA	NA	HPLC	[67]
Fermented milk	53.9	**337.1**	NA	NA	22.9	29.1	82.9	NA	HPLC	[66]
Kefir	1.6	9.6	ND	ND	12.1	2.2	4.5	ND	HPLC	[66]
FERMENTED VEGETABLES										
Fermented vegetables	**138.1**	**177.7**	**31.5**	66.0	549	316.3	154.8	83.2	HPLC, LC-MS/MS	[11,68,69]
Kimchi	**947.3**	**357.9**	23.9	74.8	428	193	550.1	83.2	LC-MS/MS	[70,71]
Sauerkraut	37.0	**206.3**	0.2	31.6	162.4	79.5	10.98	1.2	LC-MS/MS, HPLC	[72,73]
Fermented fruits	72	86.8	6.3	22.9	286.9	179.2	14.0	9.8	HPLC, LC-MS/MS	[68,70]

His: histamine, Tyr: tyramine, Phe: phenylethylamine, Trp: tryptamine, Put: putrescine, Cad: cadaverine, Spd: spermidine, Spm: spermine. ND = Not detected.
HPLC: High Performance Liquid Chromatography, IELC: Ion Exchange Liquid Chromatography; ELISA: Enzyme-linked Immunosorbent Assay.
[a] Values exceeding suggested health risk threshold shown in bold for histamine and tyramine ≥100 mg/kg and phenylethylamine ≥30 mg/kg.
[b] Persons taking medications containing monoamine oxidase inhibitors (MAOI) or using alcohol may be susceptible at lower levels. Refer to Section 2.3.

fermented soybean pastes (doubanjiang, douchi), and Indonesian fermented soybean pastes (tempeh) [26]. These foods are frequently used in a variety of processed products and are commonly consumed in some households, especially in Asian cultures [26]. Based on the literature, the amount of BAs in most fermented soybean foods are generally within the safe limits; however, there are some reports that showed both soy sauces and fermented soybean pastes may contain some BA levels above the safe dose for human consumption.

The amount of different BAs vary greatly across fermented soybean products. Based on the maximum BA levels reported, it seems very likely that occasional risk of food intoxication may occur after eating fermented soybean products, especially if the pastes contain large amounts of vasoactive BAs such as histamine, tyramine, and phenylethylamine. The maximum histamine levels in most soybean products (soy sauce, natto, miso, cheonggukjang, doenjang, sufu, and douchi) are 2–27 times higher than the suggested toxic dose. Both tyramine and phenylethylamine are reported at high levels in soy sauce, natto, cheonggukjang, doenjang, sufu, and douchi. Other fermented soybean products (ssamjang and tempeh) were not found to contain levels of histamine, tyramine or phenylethylamine above the suggested toxic dose. The maximum BA content among all soybean products reviewed here are shown in Table 3.

In the case of soy sauces, the risk may not be very significant from the high histamine, tyramine, or putrescine content, since the intake per serving is only a small quantity. However, some soybean pastes, such as natto, tempeh, and cheonggukjang, may be consumed as main dishes rather than side dishes. As main dishes, BA content may be high enough to increase the risks of food intoxication [26]. Several studies have reported the use of *Bacillus* starter cultures (*B. subtilis*, *B. licheniformis*, *B. subtilis* and *B. amyloliquefacien*) and *Pediococcus pentosaceus* strains to reduce BA formation in fermented soy bean foods [26,42,74].

2.5.2. Fermented fish products

Although histamine is the most widely investigated BA in fish products, previous exposure data show that all eight BAs reviewed here (histamine, tyramine, phenylethylamine, tryptamine, putrescine, cadaverine, spermidine, and spermine) can be found in fermented fish products [1]. Some common fermented fish products include fermented salted fish, fermented fish sauces, Malaysian fermented fish product (ikan pekasam), Korean fermented fish products (anchovy and sand lance sauces, shrimp, clam, and squid pastes) [1]. *Escherichia*, *Enterobacter*, *Salmonella*, *Shigella*, *Streptococcus*, *Lactobacillus*, *Leuconostoc* spp., and *Clostridium perfringens* are some common bacteria that have been reported to produce BA in fish [31].

Histamine, putrescine, and cadaverine have been used as quality indicators for fresh fish because their levels typically increase during the course of spoilage in fish, while the levels of spermine and spermidine decrease [32,62]. Several exposure reports found histamine, tyramine, and phenylethylamine levels in fermented fish products to be higher than the suggested toxic levels, especially in fermented salted fish, fish paste, and fish sauce (summarized in Table 3). Reported histamine levels in fermented salted fish was almost 5 times higher than the suggested toxic dose of 100 mg/kg; anchovy and sand lance sauces also have high histamine and tyramine levels [75], although not all fish species contain levels of muscle histidine associated with histamine development. Fish products containing high histamine, putrescine, and cadaverine levels are considered indicators of spoilage [76]. Even though histamine and other BAs are present at a wide range of levels in fish sauces, they might not contribute to significant health risks due to the small average intake amount [77]. However, excessive consumption of fish sauces containing high BA levels, especially with other fermented foods and drinks, may result in adverse health effects, and, therefore, have not been recommended [77].

In general, both fish and fish sauces may contain elevated BA levels, although fish sauces are reported to have higher BA levels versus other fermented fish products [1]. However, the factors contributing to BA production in fermented fish are well identified in the literature [1]. Using potent starter cultures (*Pediococcus acidilactici*, *Staphylococcus carnosus*, *Staphylococcus xylosus, Lactobacillus sake* [67]), hygienic raw materials, and improved processing methods and storage conditions may prevent or reduce the formation of excess BAs in fermented fish [1].

2.5.3. Fermented meat products

The most prevalent BAs in fermented meats are tyramine, cadaverine, putrescine, and histamine, whose levels greatly differ among different types of products. Normally, high BA levels are probable when the quality of processing conditions favor contamination or when the autochthonous microbiota present has decarboxylase potential [8]. In fresh meat, spermine and spermidine occur naturally, whereas storage may increase histamine, cadaverine, putrescine, and tyramine levels [32]. Ideally, the total BA content should not exceed 5 mg/kg in fresh meat; a total BA index between 20 and 50 mg/kg indicates meat with low-hygienic quality [32,78]. BA accumulation is common in fermented meats because of their high protein content and likelihood of undergoing amine decarboxylation from predominant microflora [79]. Unhygienic production and ripening process are suggested to be the main sources of BA contamination in fermented meat [80]. *Enterobacteriaceae*, *Lactobacillus*, *Pseudomonas*, *Micrococcus,* and *Staphylococcus* are some common BA-producing bacterial species in fermented meat [58]. Some common fermented meat products include fermented dry and soft sausages, marinated or ripened meat products, salami, ham etc.

Several studies reported the presence of all eight BAs reviewed here at varying concentrations in different types of fermented sausages [1,61,62]. Histamine, tyramine, phenylethylamine, tryptamine, putrescine, and cadaverine levels are reported to be very high in some fermented sausages and salami; the maximum histamine level was five times more than the suggested toxic dose in food (Table 3). Histamine levels in other fermented meat products (marinated beef, fermented pork) are reported to be low; however, tyramine levels are found to be over the suggested toxic dose in these products. Since fermented meat products might be consumed as main dish or in higher amounts (compared to sauces or pastes), the presence of BA levels in notable amounts may result in adverse health effects, especially for sensitive consumers. *Staphylococcus xylosus*, *Staphylococcus vitulinus, Staphylococcus hominis, Staphylococcus carnosus, Lactobacillus plantarum, Lactobacillus carvatus, Lactobacillus casei*, *Lactobacillus sakei,* and *Pediococcus pentosaceus* are examples of some amine-negative starters, which were found to suppress BA accumulation in fermented meat [67].

2.5.4. Fermented dairy products

Dairy products, especially ripened cheeses, often contain high BA levels. The "cheese reaction", as commonly referred to, is a foodborne intoxication from exposure to high tyramine [8]. The BA content in different types of cheeses varies, even among different parts of the same cheese [8]. In general, the BA concentrations are lower in short-ripened cheeses versus long-ripened cheeses [32]. Lactic acid bacteria included in the genera *Enterococcus*, *Lactobacillus*, *Leuconostoc*, *Lactococcus*, and *Streptococcus* are some common BA producers in cheese [81]. Bacteria from the *Enterococcus* and *Lactobacillus* genera are mainly responsible for BA production in cheeses made from unpasteurized milk [82]. Some common fermented dairy products include fermented cheese (e.g., blue cheese, mish cheese, cheddar cheese, feta cheese, parmesan cheese), fermented milk, yogurt, and kefir.

Elevated histamine levels over toxic threshold levels have been reported in blue cheese, mish cheese, parmesan cheese, hard cheese, semi-hard cheese, and soft cheese; however, levels below the toxic threshold occur in fermented milk, kefir, feta and cheddar cheeses. Tyramine levels are high in most fermented dairy products, such as blue cheese, feta cheese, mish cheese, hard cheese, semi-hard cheese, soft cheese, fermented milk and exceed suggested toxicological thresholds. Other dairy fermented products, including buttermilk and yogurt, are not likely to contain high BA levels [81]. A Belgian survey found that fermented dairy products tend to have higher initial concentrations of BAs, although these concentrations may remain stable or even decrease during storage due to the metabolism of BAs by certain strains of lactic acid bacteria [67].

Several studies indicate that the main approach for preventing BA accumulation is to control or reduce the amount of BA-producing microorganisms during cheese making. Implementing proper thermal treatment of milk, improving hygienic conditions, using suitable microbial starters without BA synthesis capability (such as *Brevibacterium linens*, *Lactobacillus plantarum* and *Lactobacillus paracasei* [83, 84]), and low storage temperatures are some of the ways to achieve low BA content in fermented dairy products [81].

2.5.5. Fermented fruits and vegetables

Fermentation is a traditional way of preserving vegetables and fruits in many cultures. Some traditional fruits and vegetables that are often fermented include cucumber, white cabbage (sauerkraut), red cabbage, Brussel sprout, broccoli, cauliflower, pepper, olives, beetroot, radish, white turnip, sunchoke, carrot, tomato, pumpkin, garlic, kimchi, celery, champignon, and mustard [85]. BA levels differ significantly in the literature among different fermented fruits and vegetables. Putrescine, tyramine, cadaverine, and histamine have been reported to be the dominant BAs in fermented vegetables [85].

Several studies reported high BA levels in kimchi, with maximum histamine levels – 9.5 times over the suggested toxic dose. Tyramine, putrescine, cadaverine, and spermidine were occasionally observed at high levels in some fermented vegetables and vegetable products (Table 3), whereas other BAs were not detected near suggested levels of concern.

The extent of BA accumulation in fermented fruits and vegetables depends on several factors, such as the type of the raw materials, climatic conditions, agricultural practices, and processing and storage conditions [70]. Lactobacillus brevis was identified as the species to produce high levels of tyramine in kimchi [86]. Conversely, Leuconostoc mesenteroides, Leuconostoc pentosus, Leuconostoc plantarum, Weissella cibaria, and Weissella paramesenteroides were identified as the strains not able to produce BA in kimchi [86].

2.6. Mitigation strategies to control BA formation in fermented foods

The key strategies to control BA formation in food is to reduce or control the carboxylase-positive microbial load. The prevention and reduction of biogenic amines in fermented products involve both conventional and modern methods. Conventional methods include maintaining proper sanitary conditions, food handling practices throughout food processing, and temperature control during storage to inhibit the bacteria with amino acid decarboxylase activity [11,42,87]. Moreover, several studies have indicated that addition of certain food additives or chemicals can help prevent the formation of BAs in fermented foods [14,19]. For example clove oil, sodium chloride, or a combination of both has been shown to delay and slow down the production of biogenic amines in fish muscle broth [87]. Other spices, such as garlic, have also been found to have inhibitory effects on BA production in certain fermented fish products [88]. There is evidence of cava lees and their phenolic extract and phytochemicals in purified forms or as extracts to regulate the concentration of BAs in foods [89]. Onions have been shown to have a significant inhibitory effect on several BA formation during the sauerkraut fermentation process [90]. There is also evidence that addition of rose polyphenols and spice extracts (cinnamon, anise, cloves) may inhibit BA formation in fermented sausages [88,91,83].

Modern methods for controlling biogenic amine growth in fermented foods include selecting both decarboxylase-negative and amine oxidase-positive microorganisms in starter culture that will provide impactful mitigation [92]. These starter cultures can compete to prevent the excess growth of BA-forming bacteria, while expressing enzymes that directly degrade BAs [19]. Additionally, BA formation in fermented foods can be reduced with physical and chemical treatments. The physical methods include processing and storing the food at low temperatures, using suitable food packaging such as vacuum packaging, modified atmosphere packaging, and using food irradiation or high hydrostatic pressure treated raw materials [2,93,94]. There are reports that gamma irradiation effectively reduces histamine, tyramine, cadaverine, and putrescine levels in several fermented foods [4]. Adequate treatment of milk (e.g., pasteurization) before fermentation is an important factor for reducing BA accumulation in dairy products [4].

In addition to actively preventing the formation of BAs, other contemporary methods are being developed to reduce intoxication risks. One example is the incorporation of intelligent packaging systems that facilitate visual and real-time monitoring of food freshness using a fluorescent film [94]. This was developed to monitor the freshness of seafood by detecting BAs, which are indicators of spoilage [94]. Such intelligent approaches will offer significant implications for food safety and public health and will ensure a more comprehensive and dynamic approach to maintaining the freshness and integrity of food products.

2.7. Methods for identifying BAs in fermented foods

BAs in fermented foods can be detected by two approaches, either by detecting microorganisms capable of producing BAs or by directly quantifying BAs [2]. Over the last two decades, molecular methods such as polymerase chain reaction (PCR) and deoxyribonucleic acid (DNA) hybridization have become more common methods for detecting BA-producing microorganisms due to their high sensitivity, specificity, ease, and speed [84]. Before that, traditional culture methods were employed, which included using differential media with pH indicators to identify the BA-producing strains [95]. However, traditional methods were time consuming and had many shortcomings, making molecular methods better for detecting BA-producing microorganisms [84]. Over the years, several analytical methods have been developed to test and quantify BAs in foods. Methods include biosensors, thin layer chromatography, high-performance liquid chromatography (HPLC), ultraviolet (UV) detection, or mass spectrometry detection and capillary electrophoresis. We acknowledge that we have not undertaken an exhaustive review of BA identification methods, considering that comprehensive reviews on this particular aspect have been previously conducted by other authors [96,97]. Currently, HPLC-based methods are considered the most reliable, and are commonly used to simultaneously separate, analyze, and quantify BAs with high resolution, high sensitivity, and versatility [11,62]. Rapid and semi-quantitative methods include immunoassays, flow injection analysis, and colorimetric methods [11]. Recently, untargeted metabolomics approaches are also emerging as useful methods to assess food quality, which, in turn, can be used to quantify BAs in food [98]. For hygiene assessment, the EFSA expert panel suggests monitoring the raw materials and BA concentrations at multiple points during the production process of fermented foods [11]. Overall, routine testing for BAs in food is not recommended; however, if a food is implicated in illness with adverse effects similar to those associated with BAs, HPLC methods may be used to identify the presence of any BAs in leftover foods.

2.8. Guidance for food industry and public health professionals for managing risks from BAs in fermented foods

Guidance on managing the risk from BAs in fermented foods are important for several groups. These include food safety professionals, who are responsible for inspecting and approving operators who manufacture fermented foods; public health practitioners who respond to foodborne illnesses; and operators making fermented foods. These groups are often not well informed on the health risks from BAs. It is important to note that operators include small, home-based businesses selling foods at local farmers' markets, restaurants making fermented foods in-house for service, and larger commercial businesses serving retail markets, which showcase the widespread availability of fermented foods with potentially high BA levels. Key questions are "Can fermented foods potentially cause illness?", "What are biogenic amines?", "Do we need to test for BAs?", "How do we test for BAs?", and "How do we prevent BA formation in fermented foods?". A review of BA issues by a group of public health, food safety, and industry professionals led to development of recommendations, shown in Fig. 1. The recommendations describe what BAs are, what symptoms they may cause, thresholds for illness, and when testing is indicated. This information was included in guidance for fermented vegetables, soybeans, fish and meats, i.e., sauerkraut, kimchi, natto, fesikh, miso, tempeh, and sausage [99].

Biogenic amines (BAs) can be produced by microbes in fermented foods, such as fermented soybean products, vegetables, cheeses, sausage, and fish. Normal BA intake does not cause illness as intestinal amine oxidases break down and detoxify the BAs. If large amounts of BA are ingested, or if amine oxidase activity is inhibited, then acute toxic symptoms can occur such as nausea, respiratory distress, hot flushing, sweating, heart palpitations, headache, bright red rash, burning sensations in the mouth, alterations in blood pressure, diarrhea, and hypertensive crises. The toxic effects of BA may vary between individuals, depending on individual sensitivity and on the consumption of alcohol or drugs that are monoamine oxidase inhibitory.

The main BAs are histamine, tyramine, phenylethylamine, putrescine, cadaverine and spermidine. Health Canada has set action levels for histamines in anchovies, and fermented fish sauces and pastes at 200 mg/kg and for other fish and fish products at 100 mg/

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Operators manufacturing fermented foods are not required to test for BAs in their products. Operators are recommended to list BAs as a potential chemical hazard in their food safety plan. Operators can address risks of BAs by

(1) ensuring preventative measures are in place, the facility is clean and sanitary, handling practices are hygienic to limit bacteriophages and bacteria that interfere with the culture process;
(2) optimizing the fermentation: regulating time, temperature, moisture content, salt concentrations, and storage conditions; using good quality ingredients;
(3) purchasing commercial starter culture and/or verifying quality of the starter culture;
(4) monitoring that the expected culture activity occurs within correct timeframe; and
(5) monitoring for expected pH.

If a fermented food is linked to foodborne illness in consumers, inspectors are recommended to consider testing for BAs if symptoms and onset of illness in cases fit suspected BA illness.

Fig. 1. Biogenic amines in fermented foods: Understanding the risks and mitigation strategies.

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If a fermented food is linked to foodborne illness in consumers, inspectors are recommended to consider testing for BAs if symptoms and onset of illness in cases fit suspected BA illness.

3. Conclusion

Exposure to high BA levels is associated with several adverse health effects, including respiratory, digestive, cardiovascular, and neurological disorders. BAs are present in many different fermented foods and to varying levels. There is very limited knowledge and data on BA toxicity, for either individual BA or combination, dose-response, and actual concentrations in foods, making it difficult to accurately assess health risks associated with BAs in fermented foods. However, based on the severity of the toxic effects, histamine and tyramine are considered more toxic and are relevant in terms of food safety. Reports in the literature indicate that some fermented foods including soy sauce, fish sauce, fermented sausages, kimchi etc. may accumulate high BA levels, some beyond the suggested toxic doses. Currently, regulations for BAs are lacking except for histamine content in fish and fish products due to lack of well-established toxic thresholds for other BAs in humans. The use of preventive measures, along with advancements in scientific understanding and technology, can help reduce the current risk of elevated BA levels in fermented foods. In our review, we found many articles reporting elevated levels of BAs in several fermented foods; however, the authors did not provide detailed explanations for the observed elevations. The articles primarily indicated general factors for BA development that included proteolytic enzymes generating free amino acids, the presence of microbes with decarboxylase activity, the type of raw materials utilized, product composition, additives, and specific processing and storage conditions as contributors to high BA levels. This lack of clarity creates ambiguity, and further exploration on this matter is warranted. We acknowledge that our review has limitations, as we did not specifically identify or delve into the individual limitations of all the articles included in our review. However, our primary objective in the review was to highlight the potential levels of BAs in various fermented foods when preventive measures to restrict their formation are insufficiently implemented. Furthermore, we aimed to compare the maximum levels reported over the last decade with suggested toxic thresholds to emphasize the importance of preventing the occurrence of BAs in fermented foods. While we have come across reports of various fermented foods containing elevated levels of these BAs, the potential health effects associated with these levels remain unknown, which is a significant research gap. However, there are several approaches to prevent the formation of excess BAs in fermented foods to mitigate risks including both conventional and modern methods. Since some people may be more susceptible to BA toxicity, information on their concentration in fermented foods is important and would be helpful to consumers, food industries, and health professionals.

4. Methods

Three separate searches were conducted. We first identified reviews and research studies on human health effects related to BA exposure from consuming fermented foods. Second, we identified suggested toxic doses and guidelines for different BAs, and third, we identified maximum BA levels reported in different types of fermented foods. Our inclusion criteria in the all the searches focused on finding studies relevant to the impact of BAs on human health. Both scientific and grey literature were searched to capture information relevant to this topic. Bibliographies of retrieved articles were scanned to identify more extensive information. We included English language articles published between 2012 and 2023 and included older articles when relevant to contemporary context. Publications that focused on *in vivo* and *in vitro* studies were excluded. Since fermented foods were the focus of this review, studies reporting BAs in wine and other fermented beverages were excluded. Studies were evaluated for inclusion based on the title and/or abstract. In total, 123 articles were identified and further reviewed, out of which 76 were included in this review. Inclusion criteria included relevance to the topic, clearly defined results and outcomes and access to full text.

For BAs related to human health effects, Google Scholar and PubMed databases were searched using the keywords “biogenic amines” combined with “review”, “fermented food”, “toxicity”, and “human health risk”. For thresholds and guidelines, we identified peer reviewed literature and grey literature (e.g., government reports) through Ebscohost databases (including Medline, Cinahl, Academic Search Complete, ERIC, etc.) and search engines. For contamination levels in different fermented foods, we searched Google Scholar and PubMed databases using the keywords “biogenic amines” combined with “fermented fish”, “fermented meat”, “fermented cheese”, “fermented dairy products”, “fermented soy food”, “biogenic amine formation”, “biogenic amines” and “fermented vegetables". For this section, we included articles published in 2012 or later that specifically report the highest levels of each BA in fermented foods.

Data availability statement

The data supporting the findings of this article are referenced and detailed within the manuscript. However, it is important to note that the data have not been deposited into a publicly available repository. All relevant information necessary for understanding the results presented in this publication is provided within the manuscript.

CRediT authorship contribution statement

Nikita Saha Turna: Writing – original draft. **Rena Chung:** Writing – review & editing. **Lorraine McIntyre:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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