

Significance of biogenic amines to food safety and human health

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Biogenic amines are natural antinutrition factors and are important from a hygienic point of view as they have been implicated as the causative agents in a number of food poisoning episodes, and they are able to initiate various pharmacological reactions. Histamine, putrescine, cadaverine, tyramine, tryptamine, β -phenylethylamine, spermine, and spermidine are considered to be the most important biogenic amines occurring in foods. These amines are designated as biogenic because they are formed by the action of living organisms. Histamine has been implicated as the causative agent in several outbreaks of food poisoning, while tyramine and β -phenylethylamine have been proposed as the initiators of hypertensive crisis. The toxicity of biogenic amines to chicks in terms of loss of weight and mortality was also reported. The toxicity of histamine appeared to be enhanced by the presence of other amines such as cadaverine, putrescine, and tyramine. Biogenic amines may also be considered as carcinogens because of their ability to react with nitrites to form potentially carcinogenic nitrosamines. The biogenic amine content of various foods and feed have been widely studied and found in cheese, fish and meat products, eggs and mushrooms. Food substances that have been prepared by a fermentative process, or have been exposed to microbial contamination during aging or storage, are likely to contain amines. Alcoholic beverages such as beers can contain biogenic amines, as do some other fermented foods such as sauerkraut and soy bean products. Amines were also considered as endogenous to plant substance that is commonly used for food, where some fruits and vegetables were found to contain high concentrations of various amines. © 1997 Published by Elsevier Science Ltd on behalf of the Canadian Institute of Food Science and Technology

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INTRODUCTION

Amines are basic nitrogenous compounds in which one, two or three atoms of hydrogen in ammonia are replaced by alkyl or aryl groups. The simple aliphatic monoamines are widespread. The diamine putrescine and the polyamines spermidine and spermine probably occur universally in animals and plants, and at least putrescine and spermidine are found in most bacteria (Smith, 1980). Amino acid decarboxylation is the most common mode of synthesis of amines in foods, and the aromatic amines may render a food toxic. When these amines are formed by the action of living organisms through the decarboxylation process of amino acids, they are designated biogenic.

Biogenic amines are toxic substances which cause disease in man and animal, where toxæmias resulting from ingestion of food containing biologically active amines have been reported in the world (Table 1). In spite of amines being considered as endogenous to food originating from plant matter, such as fruits and vegetables, biogenic amines are formed in other foods as a result of microbial action during aging and storage. The most important biogenic amines occurring in foods are histamine, putrescine, cadaverine, tyramine, tryptamine, β -phenylethylamine, spermine, and spermidine. Foods likely to contain biogenic amines include fish, fish products, meat products, eggs, cheeses, fermented vegetables and soy bean products, beers and wines. The factors which influence the formation of biogenic

Table 1. Amine poisoning occurring in certain countries in the world

Country	Food incriminated
Canada	Fish, Cheddar cheese
Denmark	Fish
France	Fish, Swiss cheese, Cheshire, Gruyere, ham
Germany	Fish, Gouda cheese, sauerkraut
Great Britain	Fish
Japan	Fish, chicken
Netherlands	Gouda cheese
New Zealand	Fish
United States	Fish, Swiss cheese

amines in foods include the availability of free amino acids, the presence of micro-organisms that can decarboxylate amino acids, the favorable conditions of such micro-organisms for the growth and production of their enzymes. Although amines are usually formed during a decomposition or spoilage process involving formation of free amino acids through proteolysis together with bacterial production and action of amino acid decarboxylases, higher levels of histamine may be formed before the foods appear spoiled or organoleptically unacceptable. Amino acid decarboxylation takes place by removal of the α -carboxyl group to give the corresponding amine. Amino acid decarboxylases are found in certain *Enterobacteriaceae*, *Clostridium*, *Lactobacillus*, *Streptococcus*, *Micrococcus*, and *Pseudomonas* species, among others. The biogenic amines are frequently found in high concentration in food and its byproducts, especially in that which has been subjected to deliberate or accidental bacterial contamination. It was found that biogenic amines were not significantly reduced by high temperature treatment.

CLINICAL ASPECTS AND TOXICOLOGY

Histamine, tryptamine, β -phenylethylamine, and tyramine are biologically active amines which have important physiological effects in humans, generally either psychoactive or vasoactive. Psychoactive amines affect the nervous system by acting on neural transmitters, while vasoactive amines act on the vascular system (Lovenberg, 1973). The consumption of food containing biogenic amines is responsible for many pharmacological effects (Table 2) which lead to several types of food-borne disease, including histamine poisoning (scombroid poisoning) and tyramine toxicity (cheese reaction). Harmful effects resulting from the consumption of foods rich in biogenic amines can be expected only when these amines gain access to the bloodstream (Joosten, 1988b). Amines have also been implicated as the cause of toxicity to chicks. Amines were also studied as carcinogenic precursors.

HISTAMINE POISONING

Histamine is a powerful biologically active chemical and can exert many responses within the body. Although mast cells and blood basophils contain large amounts of histamine in which it is stored in special granules, the effect of histamine does not appear unless special reactions (i.e., an allergic reaction) release it into the bloodstream. Histamine exerts its effects by binding to receptors on cellular membranes which are found in the cardiovascular system and in various secretory glands (Joosten, 1988b). Histamine can directly stimulate the heart as a result of its effect on liberation adrenaline and noradrenaline from the suprarenal gland, excites the

Table 2. Biogenic amines in foods and their pharmacological effects

Amine	Precursor	Pharmacological effects
Histamine	Histidine	Liberates adrenaline and noradrenaline Excites the smooth muscles of the uterus, the intestine, and the respiratory tract Stimulates both sensory and motor neurons Controls gastric acid secretion
Tyramine	Tyrosine	Peripheral vasoconstriction Increases the cardiac output Causes lacrimation and salivation Increases respiration Increases blood sugar level Releases noradrenaline from the sympathetic nervous system Causes migraine
Putrescine and cadaverine	Ornithine and lysine	Hypotension Bradycardia Lockjaw Paresis of the extremities Potentiate the toxicity of other amines
β -Phenylethylamine	Phenylalanine	Releases noradrenaline from the sympathetic nervous system Increases the blood pressure Causes migraine
Tryptamine	Tryptophane	Increases the blood pressure

smooth muscles of the uterus, the intestine and the respiratory tract, stimulates both sensory and motor neurons, and controls gastric acid secretion (Soll and Wollin, 1977; Taylor *et al.*, 1984; Joosten, 1988b). Thus, it is not surprising that histamine poisoning is often manifested by a wide variety of symptoms (Stratton *et al.*, 1991). Characteristic symptoms affecting the cutaneous (i.e., skin) system include rash, urticaria, edema, and localized inflammation (Taylor, 1986). Gastrointestinal involvement is characterized by nausea, vomiting, diarrhoea, and abdominal cramps (Murray *et al.*, 1982; Taylor, 1986). Other symptoms include hypotension, headache, palpitation, tingling and flushing (Gilbert *et al.*, 1980; Taylor, 1985). In severe and burning sensations cases, bronchospasms, suffocation and severe respiratory distress have been reported (Franzen and Eysell, 1969). Bartholomew *et al.* (1987) reviewed over 250 suspected incidents in Britain from 1976 to 1986 and noted that the most common symptoms were rash, diarrhoea, flushing, sweating, and headache.

Histamine poisoning can result from the ingestion of food containing unusually high levels of histamine. Fish of the families *Scombridae* and *Scomberesocidae* are commonly implicated in incidents of histamine poisoning (Taylor, 1986). These include mackerel, tunas, saury, bonito, seerfish and butterfly kingfish. Non-scombroid fish, such as sardine, pilchards, anchovies, herring and marline, have also been implicated in cases of histamine poisoning (Taylor, 1985). The level of histamine in fermented sausages could possibly be sufficient to cause a toxic response if enough quantities were consumed (Stratton *et al.*, 1991). Cases of cheese-related histamine poisoning were also reported. Cheeses that are associated with outbreaks of histamine poisoning were Gouda (Doeglas *et al.*, 1967), Swiss (Sumner *et al.*, 1985), Cheddar (Kahana and Todd, 1981), Gruyere (Taylor, 1985), and Cheshire (Uragoda and Lodha, 1979). Izquierdo-Pulido *et al.* (1994) stated that histamine poisoning has not been described for beers; however, the appearance of symptoms of a severe hypertensive crisis were described in a patient taking a monoamine oxidase inhibitor (MAOI) drug after drinking 250 ml of beer.

Histamine in foods is not necessarily hazardous. Obviously, many foods contain small amounts of histamine which can easily be tolerated. A fairly efficient detoxification system exists in the intestinal tract to metabolize ingested histamine and histamine which may be formed by intestinal bacteria. The detoxification system is composed of two distinct enzymes; diamine oxidase and histamine-*N*-methyl transferase. These enzymes convert histamine into non-toxic products. This detoxification system is adequate for handling normal dietary intakes of histamine. However, it apparently fails to detoxify the large amounts of histamine that can be ingested with spoiled scombroid fish.

Histamine metabolism is inhibited by simultaneous oral administration of other amines which could potentiate food poisoning caused by histamine through inhibiting of its metabolism. Several compounds have been reported to potentiate the biological activity of histamine in laboratory animals. Of these substances, putrescine and cadaverine occur in appreciable quantities in toxic fish (Arnold and Brown, 1978) and aged cheese (Stratton *et al.*, 1991), and in low levels in non-toxic fish (Mietz and Karmas, 1977; Kim, 1979). Effects of these substances on histamine reactions have been observed in the guinea pig or its tissues. The peroral toxicity of histamine in this animal is increased by a factor of ten when the histamine was administered 40 min after oral administration of putrescine (Parrot and Nicot, 1966) and cadaverine (Bjeldanes *et al.*, 1978; Hui and Taylor, 1985). Other biogenic amines that may act as potentiators of histamine toxicity include tyramine, tryptamine, and β -phenylethylamine (Stratton *et al.*, 1991). Spermine and spermidine, also, increase the histamine transport across the gastrointestinal wall (Jung and Bjeldanes, 1979; Chu and Bjeldanes, 1981).

Since the symptoms of histamine intoxication resemble those of scombrototoxicosis, and since scombrototoxic events have frequently been associated with the consumption of fish with high histamine content, histamine has been implicated as a scombrototoxin. However, recent studies with volunteers on the role of histamine in suspected scombrototoxicosis revealed that histamine alone is unlikely to be the causative agent of such poisoning (Clifford *et al.*, 1989), whereas no significant effects were observed even with portions of spoiled mackerel containing 300 mg histamine, or mackerel from a batch which was reported to have been associated with an incident diagnosed as scombrototoxicosis. The discrepancy might be due to the absence or presence of other synergetic biogenic amines. On the other hand, Ijomah *et al.* (1991) reported that endogenous histamine released by mast cell degranulation seems to have a significant role in the aetiology of scombrototoxicosis. However, while 90 mg histamine administered (endogenous or exogenous) in herring samples to eight healthy volunteers caused effects (headache and facial flushing) in two of them, no significant differences could be demonstrated between the ingestion of endogenous and exogenous histamine (Van Gederen *et al.*, 1991).

TYRAMINE TOXICITY

Tyramine, tryptamine, and β -phenylethylamine are included in the presser amine group which are vaso-active amines. The importance of tyramine in foods is principally due to its toxicological implications since apart from being slightly toxic in itself, the tyramine reacts with monoamine oxidase inhibitor (MAOI) drugs giving rise to hypertensive crisis (Marine-Font, 1978).

Tyramine acts mainly indirectly by releasing nor-adrenaline from the sympathetic nervous system which causes an increase of the blood pressure by peripheral vasoconstriction and by increasing the cardiac output (Joosten, 1988b). Tyramine also dilates the pupils, dilates the palpebral tissue, causes lacrimation and salivation, increases respiration and increases the blood sugar (Joosten, 1988b).

The enzyme, monoamine oxidase, oxidatively deaminates amines derived from food and plays a major role in their degradation in man before they reach the blood. The use of MAOI drugs for treatment of mental depression eliminates this detoxification process. Thus, high concentrations of presser amines (i.e., tyramine) derived from foods were accumulated in the blood leading to a hypertension crisis of patients (Blackwell, 1963; Lejonic *et al.*, 1979; Smith and Durack, 1978). Cheese was the food initially associated with hypertensive disturbances noted in patients undergoing treatment with MAOI (Asatoor *et al.*, 1963; Blackwell and Mabbit, 1965). Therefore, the increase in blood pressure is now known as the cheese reaction. The cheese reaction can cause severe headache and may induce a brain haemorrhage or heart failure (Smith, 1980). Other food, such as pickled herring (Nuessle *et al.*, 1965), meat products (Boulton *et al.*, 1970), and chicken liver (Hedberg *et al.*, 1966), are shown to cause similar hypertensive attacks.

AMINES AS CARCINOGENS

Amines were also investigated as a possible mutagenic precursor, since some amines may be nitrosated or act as precursors for other compounds capable of forming nitrosamines which are carcinogenic to various species of animals and pose a potential health hazard to humans. Domestic animals fed nitrite-preserved herring meal developed severe liver disorders which were attributed to the presence of *N*-nitrosamine as a result of the reaction between the endogenous amines of the fish meal and the added nitrite (Ender *et al.*, 1964). Trace amounts of nitrosamines of dimethylamine, diethylamine, pyrrolidine and piperidine among others were reported in many food items especially fried foods (Pensabene *et al.*, 1974; Doyle *et al.*, 1993). Putrescine and cadaverine on heating are converted to pyrrolidine and piperidine, respectively, from which *N*-nitrosopyrrolidine and *N*-nitrosopiperidine are formed by heating. Therefore, the technological process of food such as salting and smoking seems to induce nitrosamine formation, while cooking (frying) enhances their formation, since raw materials were free from nitrosamines (Doyle *et al.*, 1993).

Humans are exposed to *N*-nitrosamines through *in-vivo* nitrosation of ingested amines (Tannenbaum, 1980), where amines can form *N*-nitrosamines when

exposed to nitrite under conditions similar to those found in the stomach (Lijinsky, 1980). A reaction product of tyramine and nitrite, 3-diazotyramine, induced oral cavity cancer in rats. This mutagenic compound may be formed in the stomach, where incubation of tyramine and nitrite at 37°C and a pH of 1–2 for 60 min led to significant amounts of 3-diazotyramine (Joosten, 1988b). Other nitrosatable amines which form the most known carcinogenic *N*-nitrosamines are secondary amines such as agmatine and the polyamines spermine and spermidine, which occur widely in fish, meat and vegetable products (Smith, 1980). Generally, there was a significant increase in urinary nitrosamine following consumption of a meal containing nitrate and amines compared to a meal without additional amines (Doyle *et al.*, 1993).

TOXICITY TO CHICKS

The toxicity of biogenic amines to chicks in terms of loss of weight and mortality when administered orally in the form of bacterially spoiled fish meal was first recorded by Shifrine *et al.* (1959). The toxicity of orally administered histamine *per se* was subsequently demonstrated by producing pathological changes in the digestive tract together with tissue oedema and splenic atrophy in addition to growth depression. Moreover, gizzard erosions in broiler chicks occurred widely and have been described in numerous reports (Janssen, 1971; Halama, 1973; Lu *et al.*, 1982; Fossum *et al.*, 1988). The condition may lead to increased mortality and/or to depression of growth, but occasionally, the only effect is an increased number of gizzards found to be unfit for human consumption at meat inspection (Janssen, 1971). Bacterial infection of the gizzard wall was a common finding in chicks that had died from the disease (Fossum *et al.*, 1988). The primary cause of the gizzard lesions seemed to be biogenic amines, whereas in most field outbreaks in broilers, the gizzard erosions have been associated with the inclusion of fish meal of presumed inferior quality in the diets (Johnson and Pinedo, 1971; Harry and Tucker, 1975).

Feeding chicks a diet containing 4 mg g⁻¹ histamine resulted in the production of localized lesions in the gizzard and depressed growth rate. Supplementation of synthetic biogenic amines to the diet resulted in a significant decrease in growth and increased mortality (Morsi *et al.*, 1992; Bakker and Huisman, 1994). Feed intake and growth of the chickens fed a high content of biogenic amine-diet were less favorable compared with those fed a low level of biogenic amine-diet (Morsi *et al.*, 1992; Bakker and Huisman, 1994). However, the effect of ingesting lower levels of histamine may be augmented by other factors in the diet, such as toxic amines other than histamine (Harry and Tucker, 1979). As a result of feeding poultry on histamine-containing

diets, the egg yolks were found to contain a high concentration of histamine (778 mg kg^{-1}), which significantly decreased by storage for 3–5 days at $10\text{--}13^\circ\text{C}$ or incubation at 41°C for 30 or 60 min, as well as greater decreases occurring when the yolks were boiled for 5–10 min (Moudgal *et al.*, 1991).

BACTERIA RESPONSIBLE FOR AMINE FORMATION

Usually amine production results from the presence of bacteria that are capable of decarboxylating amino acid (Gale, 1946). Decarboxylases are found in certain *Enterobacteriaceae*, *Clostridium*, and *Lactobacillus* species among others. Histamine-forming bacteria obtained from fish implicated in scombroid poisoning were *Morganella* (*Proteus*) *morganii* (Kimata, 1961; Arnold and Brown, 1978), *Klebsiella pneumonia* (Lerke *et al.*, 1978; Taylor *et al.*, 1979), *Hafnia alvei* (Ferencik, 1970; Havelka, 1967). Moreover, *Proteus vulgaris*, *Proteus mirabilis*, *Clostridium perfringens*, *Enterobacter aerogenes*, and *Vibrio alginolyticus* have all been isolated from fish and found to produce histamine (Arnold *et al.*, 1980; Yoshinaga and Frank, 1982; Frank *et al.*, 1985). Besides, Middlebrooks *et al.* (1988) isolated 14 bacterial species with histidine decarboxylase activity from decomposed fish, including *Acinetobacter lwoffii*, *Pseudomonas putrefaciens*, and *Aeromonas hydrophila*. *Plesiomonas shigelloides*, a bacterium frequently isolated from fish and aquatic environments, has been identified as a new histamine-former in fish (Lepez-Sabater *et al.*, 1994). Psychrophilic and mesophilic halophilic histamine-forming bacteria which could grow in 12% NaCl broth have been isolated from marine fish (Okuzumi *et al.*, 1981; Yogushi *et al.*, 1990; Yatsunami and Echigo, 1992a) and have been found to produce non-volatile amines in sardine meat containing 12% NaCl (Yatsunami and Echigo, 1993). Halotolerant histamine-forming bacteria have been identified in *Staphylococcus*, *Vibrio* and *Pseudomonas* (Yatsunami and Echigo, 1991, 1992b). The micro-organisms isolated from salted semi-preserved anchovies and presented the highest histamine activity were *Morganella morganii*, two strains of *Bacillus* spp. and a strain of *Staphylococcus xylosus* with capacity to form 2123, 11 and 110 ppm after 24 h of incubation at 37°C (Rodriguez-Jerez *et al.*, 1994b). Since bacteria contain a variety of amino acid decarboxylases, it is not surprising that many other amines have also been identified in food (Lovenberg, 1973). However, little quantitative information is available for other decarboxylase activity. Middlebrooks *et al.* (1988) tested 400 bacterial isolates from decomposed fish for their lysine, arginine, or ornithine decarboxylases activity, and found that over 65% showed decarboxylase activity for one or more of these amino acids. Frank *et al.* (1985) found that decarboxylation of ornithine and lysine occurred in 38

and 92%, respectively, of the mesophilic isolates from decomposed mahimahi, while 13 and 15% of psychrophilic isolates were capable of decarboxylating ornithine and lysine, respectively. Generally, the microbial species with the capacity to form histamine and those with the capacity to form other biogenic amines are similar (Rodriguez-Jerez *et al.*, 1994b). Histamine, putrescine and cadaverine were formed during storage of sardine products containing 12% NaCl at 30°C in which the number of halotolerant bacteria varied from less than 10 to 10^4 g^{-1} (Yatsunami and Echigo, 1993).

Micro-organisms commonly found in meat products include *Pediococcus*, *Streptococcus* and *Micrococcus*. Amine-producing conformers such as *Escherichia coli* and *Klebsiella oxytoca* and related bacteria like *Morganella morganii* and *Edwardsiella* spp. as well as lactic acid bacteria like *Lactobacillus brevis*, *L. Buchneri*, *L. carnis*, *L. curvatus*, *L. divergens*, and *L. hilgardii* have been isolated from meat and meat products. According to the group D *Streptococci* are well-known producers of tyrosine decarboxylase. Amine-producing obligately heterofermentative lactic acid bacteria such as *Lactobacillus brevis*, *L. buchneri*, *L. divergens* and *L. hilgardii*, as well as the facultatively heterofermentative *L. carnis* and homofermentative *L. curvatus*, have been also isolated from meat and meat products. Edwards *et al.* (1983) found that putrescine concentrations, in intact beef, pork, lamb, and minced beef increased consistently with total aerobic viable count, but cadaverine concentrations increased only when high numbers of presumptive *Enterobacteriaceae* were present. Pure culture experiments have shown that during growth on aerobically stored pork many strains of *Enterobacteriaceae* produce appreciable amounts of cadaverine, while *Pseudomonas* produce mainly putrescine (Slemr, 1981). Edwards *et al.* (1987) showed that tyramine formation is restricted to *Lactobacilli* particularly *L. divergens* and *L. carnis*. Some *Enterococcus faecalis* strains that are isolated from meat produce tyramine, while coliform and related strains produce tyramine, putrescine, and cadaverine (Maijala *et al.*, 1993). The histamine-producing strains, especially *Hafnia alvei*, increased in the minced meat during incubation at $20\text{--}22^\circ\text{C}$ (Maijala *et al.*, 1993). Contaminant lactic acid bacteria (LAB) were tyramine and/or histamine positive and most of these strains were found in sausages at the end of ripening, in those with the highest amine levels, which may cause an increase in histamine and tyramine concentrations during sausage fermentation. It was reported that contaminant lactic acid bacteria (LAB) play an important role in amine formation during the ripening of dry sausages (Maijala and Eerola, 1993; Shalaby and Abd El-Rahman, 1995). Therefore, using a starter culture of *Lactobacillus plantarum*, which was unable to produce histamine or tyramine for manufacturing dry sausages led to a decrease in the levels of these amines from the control (Buncic *et al.*, 1993).

Many organisms may be responsible for the build-up of amines present in cheese. It appears that micro-organisms possessing active decarboxylases are adventitious organisms, rather than part of the starter culture population (Voigt and Eitenmiller, 1978). Histidine decarboxylase activity appeared to be species and strain specific. Some bacteria which are used as starter cultures in the dairy industry, such as *Streptococcus lactis* and *Lactobacillus helveticus*, are identified as histamine producers (Stratton *et al.*, 1991). Other histamine-producing organisms include *Streptococcus faecium*, *Streptococcus mitis*, *Lactobacillus bulgaricus*, *Lactobacillus plantarum*, and propionibacteria (Edwards and Sandine, 1981). *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Lactobacillus arabinose* have also been shown to possess histidine decarboxylase activity (Stratton *et al.*, 1991). Sumner *et al.* (1985) isolated from Swiss cheese a histamine-producing strain of *Lactobacillus buchneri* that is capable of producing 42 mg 100 ml⁻¹ medium. Five strains that were very similar to the histamine-producing strain of *Lactobacillus buchneri* were also isolated from Gouda cheese (Joosten and Northolt, 1989). *Enterobacteriaceae*, heterofermentative lactobacilli and *Enterococcus faecalis* were associated with considerable production up to 600 ppm of biogenic amines including β -phenylethylamine (Nout, 1994). Recently, Rodriguez-Jerez *et al.* (1994a) described the histamine activity of *Bacillus macerans* 1(3), isolated from Italian cheese samole during seasoning. This organism was capable of forming histamine at 43, 37, 30, 22 and 4°C, but the maximum histamine formation and the maximum bacterial growth were detected at 30°C, with 4285 μ g of histamine per milliliter of quantification broth.

MECHANISM OF AMINE FORMATION

Amine build-up usually results from decarboxylation of free amino acid by enzymes of bacterial origin. Amino acid decarboxylation takes place by removal of the α -carboxyl group to give the corresponding amine. Arginine is easily converted to agmatine, or as a result of bacterial activity can be degraded to ornithine from which putrescine is formed by decarboxylation. Lysine can be converted by bacterial action into cadaverine. Histidine can, under certain conditions, be decarboxylated to histamine. Tyramine, tryptamine, and β -phenylethylamine come by the same manner from tyrosine, tryptophan, and phenylalanine, respectively. Proteolysis, either autolytic or bacterial, may play a significant role in the release of free amino acids from tissue proteins which offer a substrate for decarboxylases reactions.

Two mechanisms of action, for amino acid decarboxylation, have been identified; a pyridoxal phosphate dependent reaction and a non-pyridoxal

phosphate dependent reaction (Eitenmiller and De Souza, 1984). Pyridoxal phosphate joined in a Schiff base linkage to the amino group of a lysyl residue forms the active site of the enzyme. Pyridoxal phosphate by itself can catalyse many amino acid reactions that are usually brought about by pyridoxal phosphate dependent enzymes and thus can be considered to be the portion of the enzyme that actually takes part in the reaction. The carbonyl group of pyridoxal phosphate reacts readily with amino acids to form Schiff base intermediates, which are then decarboxylated with the elimination of water to yield the corresponding amines and the original pyridoxal phosphate moiety (Eitenmiller and De Souza, 1984).

Non-pyridoxal phosphate-catalysed decarboxylation involved a pyruvoyl residue instead of pyridoxal-5-phosphate (Snell *et al.*, 1975). The pyruvoyl group is covalently bound to the amino group of a phenylalanine residue on the enzyme, and is derived from a serine residue (Recsie and Snell, 1980). Of an active proenzyme, the pyruvoyl residue acts in a manner similar to pyridoxal phosphate in the decarboxylation reaction (Eitenmiller and De Souza, 1984).

OCCURRENCE IN FOODS

Scombroid fishes and some non-scombroid fishes (e.g., sardine, pilchards, anchovies, herring and marline), as well as other foods such as meat products, cheeses, some fermented products, and some beverages, are high risk foods and certainly deserve concerned attention. Certain factors may limit the accumulation of biogenic amines in such foods. Availability of substrate, pH, salt concentration and temperature have limiting effects on the build-up of amines. The factor pyridoxal phosphate is also required for decarboxylation in some bacteria. Food additives such as potassium sorbate may be used to limit the formation of biogenic amines in foods. Biogenic amines found in certain foods along with the bacteria responsible for their production in such foods are given in Table 3. It is of interest to mention that amine levels vary extensively not only between different food varieties but also within the varieties themselves. The maximum levels of biogenic amines recorded for some selected foods are given in Table 4.

Fish and fish products

It is beyond dispute that fish and fish products have received the greatest attention in terms of biogenic amines content. Such fishes contain red muscles which are rich in free histidine varying from 1 g kg⁻¹ in herring to as much as 15 g kg⁻¹ in tuna that may be converted to histamine by the decarboxylase process. It appears to be generally accepted that the production of histamine is in itself of bacterial origin and therefore

does represent a criterion of spoilage or deterioration in fishery products. However, the production of histamine *per se* would not be expected to be detectable by simple means, e.g., change in appearance or production of off-odors, whereas fish containing large amounts of histamine may have a normal appearance and odor (Arnold and Brown, 1978). Recently, good correlation was found between expert sensory decisions for "accept/reject" quality and levels of putrescine and cadaverine in the canned skipjack tuna (Sims *et al.*, 1992).

Several studies were conducted to investigate the effect of storage temperatures on biogenic amines formation in fish. Yoshida and Nakamura (1982) found that no trace of histamine was detected in fresh fishes, but when a fresh mackerel was left to stand at room temperature, the level of histamine increased up to 28.4 ppm after 24 h and to 1540 ppm after 48 h. Also, histamine was readily formed when whole skipjack tuna was incubated at moderate and elevated temperature, although fresh fish was free from histamine (Frank *et al.*, 1981). The histamine formation was optimum at

37.8°C (100°F) and was dependent upon microbial activity. It seems that storage at low temperature reduces the rate of biogenic amines formation in fishes. Salguero and Macki (1979) found little histamine was produced even after 18 days of storage at 0°C, while at 10°C, the level of histamine exceeded 1 g kg⁻¹ tissue in both mackerel liver and muscle after 5 days' storage. The same findings were given by Murray *et al.* (1982) who mentioned that, when mackerel is allowed to spoil in ice, the level of histamine does not exceed more than 50 mg kg⁻¹ fish even when it becomes unfit to eat; while, storage at higher temperatures, especially above 10°C, led to high levels of histamine. Biogenic amines in sardines stored in the refrigerator (4–5°C) or crushed ice increased as decomposition progressed and the toxic level of histamine was developed only when sardine had an advanced stage of decomposition even when sardine was inoculated with *P. morganii* (El-Akel, 1993). Fran and Sims (1987) found that putrescine, cadaverine and histamine were developed in the raw fish (skipjack and yellowfin tuna) only after extensive holding at abusive

Table 3. Bacteria isolated and amines found in several types of foods

Food	Bacteria isolated	Amines found
Fishes	<i>Morganella morganii</i> , <i>Klebsiella pneumonia</i> , <i>Hafnia alvei</i> , <i>Proteus mirabilis</i> , <i>Proteus vulgaris</i> , <i>Clostridium perfringens</i> , <i>Enterobacter aerogenes</i> , <i>Vibrio alginolytiens</i> , <i>Bacillus</i> spp., <i>Staphylococcus xylosum</i>	Histamine, tyramine, cadaverine, putrescine, agmatine, spermine, spermidine
Cheeses	<i>Lactobacillus buchneri</i> , <i>Lactobacillus 30a</i> , <i>L. bulgaricus</i> , <i>L. plantarum</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. arabinose</i> , <i>Streptococcus faecium</i> , <i>S. mitis</i> , <i>Bacillus macerans</i> , <i>propionibacteria</i>	Histamine, cadaverine, putrescine, tyramine, β -phenylethylamine, tyryptamine
Meat and meat products	<i>Pediococcus</i> , <i>Enterobacteriaceae</i> , <i>Lactobacillus</i> , <i>Pseudomonas</i> , <i>Streptococcus</i> , <i>Micrococcus</i>	Histamine, cadaverine, putrescine, tyramine, β -phenylethylamine, tryptamine
Fermented vegetables	<i>Lactobacillus plantarum</i> , <i>Pediococci</i> sp., <i>Leuconostoc mesenteroides</i>	Histamine, cadaverine, putrescine, tyramine, tryptamine
Fermented soy products	<i>Rhizopus oligosporus</i> , <i>Trichosporon beiglli</i> , <i>Lactobacillus plantarum</i>	Histamine, cadaverine, putrescine, tyramine, tryptamine

Table 4. The highest amounts of biogenic amines recorded in available literature for selected foods^a

Species	Type	The highest amount recorded (mg 100 g ⁻¹)			
		Histamine	Putrescine	Cadaverine	Tyramine
Anchovy	Canned	1625	60	228	
	Paste	3440	37	184	
Herring	Fresh	1	6	2	
	Canned	11.7	122	35	
	Smoked		44		
Mackerel	Fresh	127	56	286	
	Frozen	0.1	1.6	0.05	
	Canned	36	35	59	
	Smoked	1788	49	252	
Tuna	Canned	2000	200	447	
Sardine	Canned	850	115	270	
Sausage	Dry	654	1506	535	151
Vegetables	Fermented	20	23	3	10
Soy products	Fermented	462	1234	634	3568

^a Various references.

conditions (e.g., 36 h at 21°C), and after the initial appearance of those diamines the rate of increase was extremely rapid. Shalaby (1990) stated that there is a general decrement trend of both spermidine and spermine concentrations in relation to other biogenic amines up to the end of storage time for each kind of fish tested (mullet, sea bream, and sardine). The ascending pattern of changes that were noticed in cadaverine, putrescine, and especially histamine was affected by the preservation conditions rather than fish species. Vacuum packaging did not show any beneficial effect in controlling bacterial growth and histamine production by *K. oxytoca* T2, *M. morganii* JM or *H. alvei* T8 in tuna stored at 2°C (Wei *et al.*, 1990). Low temperature storage was more effective than vacuum packaging in controlling histamine production by bacteria tested, since samples stored at 10°C showed significant bacterial growth and had higher levels of histamine ($> 2 \text{ g kg}^{-1}$) than those stored at 2°C.

Mietz and Karmas (1977) showed that histamine has frequently been used as an indicator of decomposition in fresh tuna prior to canning, but itself has not always proved useful. They suggested an index from the individual amines. Such an index was compared favorably to organoleptic and authentic pack value scores. The formation of putrescine, cadaverine, and histamine, and the loss of spermidine and spermine were observed by Mietz and Karmas (1978) as decomposition of tuna progressed, and also that these amines serve as quality indicators of tuna. Recently, principal component analysis was used for processing the biogenic amine data obtained from the HPLC method (Lebiedzinska *et al.*, 1991). The results indicated that this multivariate statistical method greatly assisted the assessment of the quality of fish samples.

Biogenic amines could be produced in the musculature of mackerels and sardines during storage under frozen conditions at -20°C (Tiecco *et al.*, 1984). Histamine was found in all frozen fish (52 samples) tested by Pechanek *et al.* (1983). On the contrary, Hardy and Smith (1976) reported that while the rate of histamine production was much less in the mackerel fish held in ice, no histamine was detected up to 72 weeks of storage at -14, -12, or -29°C. Also, biogenic amines content of tuna fish and mackerel did not alter during storage at -18°C (Schulze and Zimmermann, 1982). During thawing of frozen fish, the biogenic amines content showed a fluctuating pattern of changes (Abdalla *et al.*, 1990) as a net result between rate of formation which depends on the endoenzymes of fish tissue and the enzymes of the micro-organisms (Arnold and Brown, 1978; Eitenmiller and De Souza, 1984), and the rate of breakdown which depends on the capability of bacteria for consuming the resulting amines (Janz, 1985a,b; Scheibner, 1987).

Histamine was hardly formed during salting due to the inhibitory effect of salt upon histidine decarboxylase

activity (Kang and Park, 1984). However, halotolerant bacteria produced biogenic amines in sardine meat containing 12% NaCl (Yatsunami and Echigo, 1993), as well as histamine content, increased throughout the curing period of fish products (Wada and Koizumi, 1986; Shalaby, 1990), and was detected in salted and pickled fish samples (Pechanek *et al.*, 1983; Askar *et al.*, 1986; Shalaby, 1995).

Some histamine, formed during storage of fish, is partially lost during the canning process (Shalaby, 1990), but the losses are considered not to be sufficient to enable such fish to become passable when canned (Arnold and Brown, 1978). The biogenic amine content of fish products was not significantly reduced by sterilization during the canning process (Durr *et al.*, 1980; Shalaby, 1990), since about 90% of the biogenic amines is recovered from tuna and mackerel after sterilization (Luten *et al.*, 1992). On the contrary, Fran and Sims (1987) stated that the conditions of precooking and subsequent heat processing (retorting) of canned tuna significantly lowered the levels of biogenic amines, but whenever putrescine and cadaverine levels were found in canned tuna at amounts above background levels, the implications were important, indicating that the original raw material had reached a stage of advanced decomposition. Generally, the histamine content of canned fish is affected by freshness of fish, fish species, chilling conditions of transportation, and precooking methods (Tuan and Tsai, 1981).

Since amines are formed by the bacteria flora of food material prevention of bacterial growth and/or inhibition of such amine production would be very important for food safety. Taylor and Speckhard (1984) found that potassium sorbate (0.5%) inhibited both the growth and histamine production by selected strains of *P. morganii* and *K. pneumonia*, while sodium hexametaphosphate (2%) slowed down the rate of histamine production in trypticase soy histidine broth. When sardine was treated by these preservatives and stored in refrigeration, a putrefactive odor developed within two days of storage (El-Akel, 1993). The addition of acidulants such as citric acid, malic acid and succinic acid as well as D-sorbitol inhibited histamine formation and histidine decarboxylase activity in mackerel stored at 25°C for 10 days (Kang and Park, 1984). The effect of spices on growth of and biogenic amine formation by *Enterobacter aerogenes* and *M. morganii* was also studied (Wendakoon and Sakaguchi, 1992). Clove and cinnamon were found to be the most effective against biogenic amine formation rather than bacterial growth.

Meat and meat products

Meat and meat products have been reported to contain tyramine, cadaverine, putrescine, spermine, and spermidine (Koehler and Eitenmiller, 1978; Nakamura *et al.*, 1979; Edwards *et al.*, 1983; Santos-Buelga *et al.*,

1986; Stratton *et al.*, 1991; Shalaby, 1993, 1994, 1995). Fermentation may be important in the formation of histamine in certain types of sausages. Semi-dry sausages are fermented for short periods often with lactic acid cultures added, while dry sausages are allowed to ferment from the action of natural microflora for a longer period (Genigeorgis, 1976). During the sausage ripening process, the histamine concentration increases at least ten-fold during the first three days of ripening (Dierick *et al.*, 1974). In general, quite variable quantities of biogenic amines were reported for sausages. The variable concentration could be due to the variation of the ripening process time (Cantoni *et al.*, 1974), the variation and difference of decarboxylase activity of the natural microflora responsible for fermentation, and the biosynthesis and metabolism of such amines (Askar, 1979; Shalaby and Abd El-Rahman, 1995) in addition to variations in the manufacturing process, the great variation in the type and quality of the meat used, the proportion of meat content included, and the length of maturation (Shalaby, 1995).

Fresh pork samples contain spermine, spermidine, and traces of other amines. Increases in the biogenic amine content of pork are temperature dependent. During storage, biogenic amine concentration increases, while both spermine and spermidine concentration decreases. Pork stored at 30°C had higher biogenic amine levels than pork stored at 4°C, while biogenic amine levels of pork stored at -18°C did not alter over a 9-month period (Chen *et al.*, 1994). Significant increases in biogenic amine concentrations were associated with spoilage (Nemeth-Szerdahelyi *et al.*, 1993). Levels of putrescine, cadaverine, and histamine were significantly correlated with the volatile basic-N (VB-N) values of pork. Therefore, freshness of pork can be judged accurately on the basis of amine content combined with VB-N values of <20 mg g⁻¹ (Chen *et al.*, 1994). Biogenic amines were also formed in fresh vacuum-packaged beef during storage at 1°C for 120 days. Significant levels were detected starting at Day 20 of storage. It was also reported that although cold stored vacuum-packaged beef was sensorially acceptable, it could pose some risk to individuals sensitive to biogenic amines (Smith *et al.*, 1993).

Cheeses

Usually cheeses do not contain biogenic amines but sometimes very high levels are formed (Joosten and Stadhouders, 1987). Biogenic amines have been found in small amounts in dried milk (Voigt *et al.*, 1974) and in large quantities in many cheese varieties (El-zayat and El-Bagoury, 1988; Stratton *et al.*, 1991). The most important biogenic amines occurring in cheeses are tyramine, histamine, putrescine, cadaverine, tryptamine, and β -phenylethylamine (Joosten, 1988a; Tawfik *et al.*, 1992). During cheese ripening, casein is slowly degraded

by proteolytic enzymes, leading to an increase of free amino acids content (Foster *et al.*, 1958; Joosten and Olieman, 1986), which can be subjected to subsequent breakdown reactions and catalysed by specific bacterial decarboxylases to give rise to the formation of CO₂ and an amine. Therefore, biogenic amines are gradually increased with different levels especially histamine, putrescine, and cadaverine, by extending cheese ripening time (Degheidi *et al.*, 1992). Processed cheeses which are subjected to high temperature during manufacturing contained appreciable levels of biogenic amines (Spanjer and Van Roode, 1991; El-Sayed, 1996).

Other fermented foods

Fermented soy beans products such as miso, soy souse, and tempe have been popular in the Orient for more than one thousand years and are becoming increasingly popular in Western countries. Since several varieties of molds, yeasts, and lactic acid bacteria are involved in the fermentation processes of such products and the raw materials (soy beans, legumes, cereals or other suitable raw materials) contain considerable amounts of protein, the formation of various amines might be expected during the fermentation (Chin and Koehler, 1983). Tyramine and histamine have been found at various levels in such products (Stratton *et al.*, 1991). High levels of biogenic amines (1 g kg⁻¹) were reported for soy sauce made from black soy bean (Yen, 1986), while tyramine has been found at moderately high levels (450 mg kg⁻¹) in fermented salted black beans (Mower and Bhagavan, 1989). The variability of biogenic amines levels in the commercial fermented soy products samples could be attributed to variability in the ratio of soy bean to other seeds used in the raw material, the microbiological composition and the conditions and duration of fermentation (Chin and Koehler, 1983; Nout *et al.*, 1993). Nout *et al.* (1993) showed that the functional fungus of tempe, *Rhizopus oligosporus*, mainly produced tyramine and some putrescine, but both *Klebsiella pneumonia* and *Trichosporon beiglii* led to increased total biogenic amines in the tempe, while *Lactobacillus plantarum* reduced tyramine levels in that product.

Fermented vegetables represent another class of foods from which biogenic amines have been isolated. Small amounts of biogenic amines could be detected in fermented vegetables following inoculation with *L. plantarum* (Andersson, 1988). The main biogenic amines in sauerkraut are histamine, tyramine, putrescine and cadaverine, while β -phenylethylamine is found only in minor quantities. Screening tests revealed that commercial sauerkraut products contained considerable amounts of biogenic amines — 540 mg kg⁻¹ (Kuensh *et al.*, 1989). Joosten and Olieman (1986) indicated that a sauerkraut extract contained a large amount of putrescine (210 mg kg⁻¹), as well as tyramine, histamine and

cadaverine and were detected with concentrations of 69, 58 and 79 mg kg⁻¹, respectively. The average histamine level of the retail sauerkraut samples was 51 mg kg⁻¹ (Taylor *et al.*, 1978a). Although sauerkraut routinely contains levels of histamine far below the toxic dose of 1 g kg⁻¹ (Stratton *et al.*, 1991), it has been implicated in an incident of histamine poisoning in Europe (Mower and Bhagavan, 1989), indicating that sauerkraut has been suspected to occasionally contain amounts of histamine near the toxic dose. Sauerkraut fermentation studies (Kuenst *et al.*, 1989) indicated that considerable amounts of putrescine (150 mg kg⁻¹) were formed during the initial stage which was paralleled to the decrease in arginine concentration, while histamine and tyramine appeared at the final period of fermentation. Accordingly, the production of sauerkraut which is low in histamine can be achieved by minimizing the fermentation period.

Occasionally, fermented beverages, such as beers, contain histamine and other biogenic amines which are responsible for the episodes of headaches and flushing sometimes experienced after their ingestion (Stratton *et al.*, 1991). Histamine has been found at high concentrations reaching 4.7, 15, and 20 mg l⁻¹ in Swedish, Danish, and French beers, respectively (Granerus *et al.*, 1969; Zee and Simard, 1981). Tyramine was also detected by levels as high as 11 mg l⁻¹ in beers of various origin (Maga, 1978). Putrescine and cadaverine levels are generally low in beers (Stratton *et al.*, 1991). Agmatine, putrescine, and tyramine were found at concentrations ranging from 0.55 to 67.60 mg l⁻¹, while histamine, tryptamine, β -phenylethylamine, cadaverine, spermine, and spermidine showed levels lower than 2 mg l⁻¹, but relatively high concentrations of histamine and cadaverine were detected in some European beers (Izquierdo-Pulido *et al.*, 1994). Since brewer's yeast seems to lack the ability for producing amines during fermentation, biogenic amines in beers can be related to the raw materials and/or to microbial contaminations during brewing.

Fresh fruits and vegetables

Amines are endogenous to a plant substance that is commonly used for food and were found to be widespread in fruits and vegetables (Lovenberg, 1973). Surprisingly, not many investigators have extensively analyzed fruits for their amine content, and the available data indicate that varieties of the same fruit can have varying amine levels (Maga, 1978). Recently, Maxa and Brandes (1993) found that putrescine was the predominant amine in most fruit juice samples including raspberries, lemons, grapefruit, mandarins, strawberries, currants and grapes. Histamine was low in these juices, except in a lemon juice sample (0.36 mg l⁻¹). Raspberry juice had a high tyramine concentration of 66.66 mg l⁻¹. Vegetables represent another plant food from which amines have been identified. Chinese

cabbage, endive, iceberg lettuce and radicchio were found to contain amines with concentration ranging from 14 to 20 μ g g⁻¹, spermidine was found to be the major polyamine presented in these vegetables since it was detected at a concentration of 7–15 μ g g⁻¹ (Simon-Sarkadi and Holzapfel, 1994). Biogenic amine levels in straw mushrooms (*Volvariella volvacea*) were found to increase with storage time at both 4 and 25°C, but reduction by about 80% was obtained after boiling for 5 min. Commercial canned mushrooms were found to contain a total of 7.1 mg kg⁻¹ of putrescine, tyramine and β -phenylethylamine (Yen, 1992).

ANALYTICAL METHODS

Studies of the occurrence of biogenic amines as well as controlling its limits in foods and food products would not be possible without the supporting analytical methods which should be standardized and harmonized by different analysts. Various methods have been published to isolate and estimate amines, but there is no single quantitative analytical method for the determination of biogenic amines in all foods. The complex sample matrix, the presence of potentially interfering compounds and the occurrence of several biogenic amines simultaneously in the same aliquot of an extract are typical problems encountered in the analysis of food for biogenic amines. Reagents such as perchloric acid, trichloroacetic acid (TCA), hydrochloric acid, and organic solvents are commonly used for the extraction of amines from foods. Various analytical techniques have been developed for the separation of biogenic amines in foods and have been reviewed (Treptow and Askar, 1990). Paper chromatography, thin layer chromatography (TLC), gas liquid chromatography (GLC), and high performance liquid chromatography (HPLC) have all been advocated for the separation and identification of amines or amine derivatives. However, interference by several unidentified factors has often necessitated the inclusion of additional chromatographic separation steps (Ough, 1971; Voigt *et al.*, 1974; Lerke and Bell, 1976).

Fluorometric methods have been used for the determination of amines individually. The currently accepted method for determining histamine in fish (AOAC, 1990) was originally developed by Staruszkiewicz *et al.* (1977) and involved extraction of the sample with methanol, separation of histamine from interfering substances using an ion-exchange column, and reaction with *o*-phthalaldehyde (OPA) under carefully controlled conditions followed by fluorometric measurement. Lerke and Bell (1976) developed a very similar procedure to the AOAC method, where 10% TCA and cation exchange resin were used instead of methanol and the anionic exchange resin of the AOAC method. Taylor *et al.* (1978b) replaced the ion-exchange clean-up step of

the AOAC method by sequential extraction. A similar method is used for the determination of tyramine in food, where after an appropriate extraction procedure, tyramine is cleaned up by ion-exchange and detected fluorometrically after its reaction with α -nitroso- β -naphthol (Santos-Buelga *et al.*, 1981).

Since biogenic amines often occur simultaneously in the same extract, analytical procedures that permit the separation and estimation of these compounds in the same aliquot of an extract are desirable. Therefore, UPLC, GLC and amino acid analyzer were used for the separation and determination of a lot of biogenic amines in foods. A wide variation of sample preparation, separation and determination techniques have been performed. Mietz and Karmas (1978) developed a HPLC method for simultaneous analysis of histamine, cadaverine, putrescine, spermidine and spermine in fish after reaction with dansyl chloride. Pre-column derivatization was also used by Hui and Taylor (1985) for the simultaneous determination of histamine, tyramine, cadaverine, putrescine, tryptamine and phenylethylamine by HPLC in both cheese and fish. After extraction of amines from sausages, nine dansylated biogenic amines are separated and determined by HPLC (Eerola *et al.*, 1993). Such methods require a derivatization step and hence a laborious clean up, as well as incomplete derivatization, can occur and side-products may be formed during the derivatization. Therefore, post-column derivatization methods were developed for determining biogenic amines in cheese, wine and sauerkraut (Joosten and Olieman, 1986) by incorporation of ninhydrin in the eluent, letting the reaction take place after the separation simply by heating. Post-column derivatization with *o*-phthalaldehyde and 3-mercaptopropionic acid was used for determining histamine, tyramine, cadaverine, putrescine and phenylethylamine in meat products by HPLC (Straub *et al.*, 1993). Developments in amine analysis are continued and both GLC (Staruszkiewicz and Bond, 1981) and amino acid analyzer (Simon-Sarkadi and Holzapfel, 1994) are used in the determination of biogenic amines in foods.

HPLC and GLC methods are quite valuable in food analysis and allow the simultaneous determination of histamine and other putrefactive amines in foods which may serve as potentiators of histamine toxicity, and hence its analysis could assume great importance (Taylor, 1985). However, many problems can occur during analysis, as well as the mobile phase, whether solvent or carrier gas, limiting applications, since the mobile phase might reduce the detector response to an analyte by dilution or salvation, while TLC permits the detection of analytes in the absence of the mobile phase, therefore, it can be more sensitive (Shalaby, 1996). In general, such methods are fairly simple, sufficiently sensitive and quantitative, and require expensive instrumentation which is not available in all testing laboratories. The analysts, on the other hand, especially public

analysts, have always been accountable to the courts for the quality and reliability of their work, in the time where there has been a steady reduction in resources for enforcement analysis (Harrison, 1995). So, an accurate, economic, and rapid analytical method is urgently needed. TLC is by far one of the most common analytical methods used to achieve such purposes. Visual comparison TLC method is the choice for a rough and quick estimation, while TLC densitometry is the choice for best quantitative results. Therefore, the TLC method (Shalaby, 1994) which offers a simple but effective and accurate means for separation and estimation of eight biogenic amines in foods could be considered, but the time required to perform this method is so long.

Generally, the methods used for analysis of food for amines individually are extremely difficult and time consuming; the time required for the separation and determination of a lot of biogenic amines is also long. Carriers (trucks, coolers, ships, etc.) which transport foods to processing plants or to markets cannot be detained for a lengthy determination, and the elapsed time will permit more development of amines, so inaccurate results will be obtained. Therefore, speed and ruggedness can sometimes be much more important than strict accuracy. So, the semiquantitative TLC technique (Shalaby, 1995), which has many advantages such as simplicity, versatility, applicability to a large number of samples in minimal time, cheapness in terms of reagents and equipment, and applicability to food in general, may be a useful technique for routine control, and can be put to use by regulatory agencies and food industries for determining the quality of food with respect to biogenic amines. However, developments and improvements should be subjected to such methods to obtain a rapid and accurate analytical technique. Improvements should be made in extracting solvents, extract clean-up steps, derivatives formation, eluting solvents, and the determination step. It could be mentioned here that development would not have been possible without the extraordinary degree of cooperation that exists among investigators in government and industry. In this concern, an organized program will be required under the care of an international agency for such purpose. Such a program will also offer the possibility of registration of biogenic amine data in the world, especially for countries with a lack of such data, in addition to establishing a standardized and harmonized analytical method.

PERMISSIBLE LIMITS

The quality criteria with respect to the presence of histamine and other biogenic amines in foods and food products are necessary from a toxicological point of view as well as from a technological point of view. The existence of potentiators could dramatically influence

Table 5. Tolerance levels of biogenic amines in foods

Food	Maximum amounts (mg kg ⁻¹)						Reference
	His.	Cad.	Put.	Tyr.	β -Phen.	Total	
General	— 50–100 — —	— — — —	— — — —	— 100–800 — 6	— 30 3 —	40 ^a — — —	Ayres <i>et al.</i> , 1980 Nout, 1994 Sandler <i>et al.</i> , 1974 Blackwell and Mabbity, 1965
Fish	—	—	—	—	—	300 ^b	Spanjer and Van Roode, 1991
Canned tuna	—	0.5	—	—	—	—	Sims <i>et al.</i> , 1992
Cheese	—	—	—	—	—	900 ^c	Spanjer and Van Roode, 1991
Sauerkraut	10	25	50	20	5	—	Kuensch <i>et al.</i> , 1989

^aAs total biogenic amines per meal.

^bSum of histamine + cadaverine + putrescine.

^cSum of histamine + cadaverine + putrescine + tyramine.

the threshold toxic dose for histamine in foods (Taylor *et al.*, 1984). Since different foods and even different types within the same food might be expected to vary in the type and amount of the various potentiators, the threshold toxic dose for histamine would be expected to vary from food to food and from type to type. The differences in type and amount of potentiators would be predicted from expected differences in the types of microflora, the metabolic capabilities of the microflora, and conditions of spoilage, aging or ripening. The other additional risk factors such as, for example, amine oxidase-inhibiting drugs, alcohol and gastrointestinal diseases may play an important role in determining the threshold for histamine and other amines (Table 5). Therefore, different oral toxic levels have been suggested. In general, 8–40 mg histamine can cause slight, over 40 mg, moderate, and over 100 mg, severe poisoning, whereas 1080 mg tyramine can cause toxic swelling and over 100 mg may cause migraine (Askar and Terptow, 1986). On the basis of the findings of Bartholomew *et al.* (1987) that depending on a survey of scombrototoxic fish poisoning in Britain which involved 250 suspected incidents from 1976 to 1986, the guidelines for histamine content of fish are <5 mg 100 g⁻¹ (safe for consumption), 5–20 mg 100 g⁻¹ (possibly toxic), 20–100 mg 100 g⁻¹ (probably toxic), and >100 mg 100 g⁻¹ (toxic and unsafe for consumption).

An intake of >40 mg biogenic amines per meal has been considered potentially toxic (Ayres *et al.*, 1980). However, not all amines are equally toxic, consequently histamine, tyramine, and β -phenylethylamine are of concern. Approximately 1000 ppm histamine is supposed to elicit toxicity. However, over half the reported scombrototoxicosis incidents in the years 1976–1986 were associated with histamine concentrations below 50 ppm. With regards to possible health hazards, the biogenic amines should be seen as an important quality factor. From a "Good Manufacturing Practice" point of view, levels of 50–100, 100–800, and 30 ppm for histamine, tyramine, and β -phenylethylamine, respectively, or a

total of 100–200 ppm are regarded as acceptable (Nout, 1994). Kuensch *et al.* (1989) proposed the following limits for fermented sauerkraut: histamine, 10 mg kg⁻¹; tyramine, 20 mg kg⁻¹; β -phenylethylamine, 5 mg kg⁻¹; putrescine, 50 mg kg⁻¹; and cadaverine, 25 mg kg⁻¹. Spanjer and Van Roode (1991) suggested that for regulation purposes, in fish and fish products, the sum of histamine, putrescine and cadaverine should be limited to 300 mg kg⁻¹. In cheese samples and sauerkraut tyramine also has to be accounted for, resulting in the suggestion that the sum of tyramine, histamine, putrescine and cadaverine should not exceed the amount of 300 mg kg⁻¹.

Some countries have regulated the maximum amount of histamine in some products. Switzerland considered 10 mg histamine per liter wine of as a permissible limit. The US Food and Drug Administration (FDA, 1982) established regulations for canned albacore, skipjack and yellowfin tunas that consider 20 mg histamine per 100 g as an indication of prior mishandling "decomposed" and 50 mg histamine per 100 g as an indication of a potential health hazard "danger to health". These regulations were expanded to include mahimahi (dolphin fish). The European Economic Community (EEC) has recently established regulation for species of fish belonging to the *Scombridae* and *Clupeidae* families and fixed a three-class plan for maximum allowable levels of histamine in fresh fish ($n=9$; $c=2$; $m=100$ ppm; $M=200$ ppm) and enzymatically ripened fish products ($n=9$; $c=2$; $m=200$ ppm; $M=400$ ppm) where n is the number of units to be analyzed from each lot, m and M are the histamine tolerances, and c is the number of units allowed to contain a histamine level higher than m but lower than M (Anon., 1991).

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