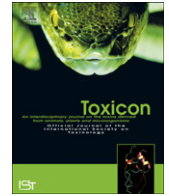




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## Scombroid poisoning: A review

James M. Hungerford\*

ATC, PRL-NW, USFDA, 22201 23rd Dr S.E. Bothell, WA 98021, United States

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### ABSTRACT

Scombroid poisoning, also called histamine fish poisoning, is an allergy-like form of food poisoning that continues to be a major problem in seafood safety. The exact role of histamine in scombroid poisoning is not straightforward. Deviations from the expected dose-response have led to the advancement of various possible mechanisms of toxicity, none of them proven. Histamine action levels are used in regulation until more is known about the mechanism of scombroid poisoning. Scombroid poisoning and histamine are correlated but complicated. Victims of scombroid poisoning respond well to antihistamines, and chemical analyses of fish implicated in scombroid poisoning generally reveal elevated levels of histamine. Scombroid poisoning is unique among the seafood toxins since it results from product mishandling rather than contamination from other trophic levels. Inadequate cooling following harvest promotes bacterial histamine production, and can result in outbreaks of scombroid poisoning. Fish with high levels of free histidine, the enzyme substrate converted to histamine by bacterial histidine decarboxylase, are those most often implicated in scombroid poisoning. Laboratory methods and screening methods for detecting histamine are available in abundance, but need to be compared and validated to harmonize testing. Successful field testing, including dockside or on-board testing needed to augment HACCP efforts will have to integrate rapid and simplified detection methods with simplified and rapid sampling and extraction. Otherwise, time-consuming sample preparation reduces the impact of gains in detection speed on the overall analysis time.

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### 1. Introduction

Scombroid poisoning, or histamine fish poisoning, is a type of food poisoning with symptoms and treatment similar to those associated with seafood allergies. Scombroid poisoning results from consumption of mishandled fish. Histamine (2-(1H-imidazol-4-yl) ethanamine) and other decomposition products are generated in time-temperature abused raw fish by bacterial, enzymatic conversion of free histidine (Rawles et al., 1996). Although high levels of histamine are generally found in the implicated fish, neither histamine fish poisoning nor scombroid poisoning fully capture the nature of this intoxication

(Lehane and Olley, 2000). The term “scombroid” derives from the type of fish (i.e. Scombridae) first implicated, such as tuna and mackerel. What these (scombrid) fish share in common are high levels of free histidine in their muscle tissues (Suyama and Yoshizawa, 1973; Perez-Martin et al., 1988; Ruiz-Capillas and Moral, 2004). It is now known that other (non-scombroid) fish species are also implicated in scombroid poisoning, such as mahi-mahi (*Coryphaena* spp.), sardines (*Sardinella* spp.), pilchards (*Sardina pilchardus*), anchovies (*Engraulis* spp.), herring (*Clupea* spp.), marlin (*Makaira* spp.) bluefish (*Pomatomus* spp.) (Taylor, 1986; Hwang et al., 1997), Western Australian salmon (*Arripis truttaceus*), sockeye salmon (*Oncorhynchus nerka*), amberjack (*Seriola* spp.) Cape yellowtail (*Seriola lalandii*), (Lange, 1988; Muller et al., 1992; Smart, 1992; Gessner et al., 1996) and swordfish (*Xiphias gladius*) (Chang et al., 2008). Most of these fish species are rich in free histidine (Lukton

\* Tel.: +1 425 483 4894; fax: +1 425 483 4996.

E-mail address: [James.Hungerford@fda.hhs.fda.gov](mailto:James.Hungerford@fda.hhs.fda.gov)

and Olcott, 1958; Taylor, 1986; Antoine et al., 1999) with salmon and swordfish being exceptions (Lukton and Olcott, 1958; Suzuki et al., 1987).

Scombroid poisoning is clearly associated with elevated histamine levels in the outbreak-associated samples (Taylor, 1986). However, there is not a clear dose-response relationship between oral administration of histamine, and histamine levels ingested in the decomposed fish, with scombrototoxic fish showing higher toxicity than an equivalent oral dose of pure histamine (Taylor et al., 1984; Taylor, 1986; Lehane and Olley, 2000). Thus scombroid poisoning is not uncomplicated histamine poisoning (Taylor et al., 1989; Lehane and Olley, 2000).

## 2. Symptoms, reporting, and treatment of scombroid poisoning

The onset of scombroid poisoning is typically from 10 min to 1 h following consumption of poisonous fish (Ansdell, 2008). The symptoms (Arnold and Brown, 1978; Kim, 1979; Gilbert et al., 1980; Taylor, 1986) are variable and include peppery or metallic taste, oral numbness, headache, dizziness, palpitations, rapid and weak pulse (low blood pressure), difficulty in swallowing, and thirst. Noteworthy as allergy-like are symptoms such as hives, rash, flushing and facial swelling (Kim, 1979; Taylor et al., 1989). Symptoms involving the central nervous system (CNS) such as anxiety (Russell and Maretic, 1986; Sabroe and Kobza Black, 1998; Specht, 1998) are less frequently observed. Less specific symptoms such as nausea, vomiting, abdominal cramps and diarrhea are also experienced (Gilbert et al., 1980).

Recovery is usually complete within 24 h, but in rare cases can last for days (Taylor, 1986). Rarely are serious cardiac and respiratory complications observed, and then for individuals with preexisting conditions (Russell and Maretic, 1986; Taylor et al., 1989; Ascione et al., 1997). In a few unusual cases hospitalization, including treatment for anaphylactic shock has been required (Sanchez-Guerrero et al., 1997; Otani et al., 2004). There are wide variations between the sensitivities of individuals to scombroid poisoning (Motil and Scrimshaw, 1979). A key aspect of the epidemiology, and in some cases the early diagnosis of histamine poisoning versus seafood allergy, is attack rate; The majority of individuals eating the same meal will respond to scombrototoxic fish, but only a small percentage of illnesses are expected if the observed symptoms are due to an allergy (Taylor et al., 1989).

It is believed that scombroid poisoning is underreported (Taylor et al., 1989; Gellert et al., 1992; Wu et al., 1997). Furthermore, apart from clues in the medical history such as the absence of allergies to seafood or other meal ingredients, small scale outbreaks may be reported as allergies unless histamine concentrations in the implicated meal remnants or plasma histamine levels are determined (Taylor et al., 1989). Treatment of scombroid poisoning includes administration of antihistamines (Lerke et al., 1978; Blakesley, 1983; Guss, 1998). Response to antihistamines by those suffering scombroid poisoning lends further support to a role for histamine in this intoxication (Taylor et al., 1989).

## 3. Histamine physiological role and metabolism

Histamine is a messenger molecule in the human body and thus not a natural toxin per se. It is ubiquitous in its distribution and released from mast cells, enterochromaffin-like cells, and neurons. Histamine targets a range of “histaminergic” receptors and its various actions are mediated by histamine receptors H1, H2, H3 and H4 and histamine has many vital functions in healthy individuals ranging from control of gastric acid secretion to neurotransmission in the central nervous system (Katzung, 2007; Maintz and Novak, 2007). Other vital roles of histamine include mediation of vascular permeability and mucus secretion, immunomodulation, hematopoiesis, wound healing, day-night rhythm, the regulation of histamine- and polyamine-induced cell proliferation and angiogenesis in tumor models (Kusche et al., 1980; Raitel et al., 1998), and intestinal ischemia (Kalchmair et al., 2003). For many, the most familiar and dramatic observable response to histamine involves the immune system and, more specifically, allergic responses (White, 1990).

These multiple roles of histamine as a naturally occurring messenger in the human body have broad implications for understanding the true nature of scombroid poisoning, especially the mechanistic aspects of scombroid poisoning and its treatment. Some responses mediated by histamine and its receptors, such as vasodilatation, smooth muscle cell contraction, alterations of blood pressure, stimulation of nociceptive nerve fibers, tachycardia, and arrhythmias, appear to correlate with the symptoms of scombroid poisoning. The H1 and H2 receptors mediate responses recognizable from scombroid poisoning symptoms such as hives, itching, and flushing (Maintz and Novak, 2007) and also actions on the cardiovascular system (Taylor, 1986). Although not included in the discussion of scombroid poisoning symptoms (Taylor, 1986) since they were discovered more recently, the H3 receptors modulate neurotransmitter release in the central nervous system and are known to cause headache, nausea, and vomiting (Maintz and Novak, 2007). Similarly, although less is known about them, the H4 receptors may play a role in scombroid poisoning and should not be discounted. Besides these specific histaminergic receptors, histamine also binds to the cytochrome P450s (CYP450) a crucial set of metabolic enzymes, (Brandes et al., 1998).

Given the role of histamine in scombroid poisoning (Taylor et al., 1989) histamine metabolism in the human body is clearly relevant to all hypothesized mechanisms for this intoxication. Diamine oxidase (DAO) and histamine N-methyl transferase (HNMT) are the two enzymes metabolizing histamine in humans (Brown et al., 1959; Bieganski et al., 1980, 1983; Maintz and Novak, 2007). DAO is not localized in the cytosol as is HNMT (Brown et al., 1959) and is excreted directly into the circulation (Schwelberger et al., 1998). Thus DAO is considered the major enzyme in histamine catabolism (Bieganski et al., 1980, 1983), responsible for scavenging extracellular histamine, including after the ingestion of histamine-rich food. Inference with these enzymes can have serious consequences, as shown by the action of various drugs which inhibit DAO (Sattler et al., 1985; Sattler and Lorenz, 1990; Novotny et al., 1994) or

HNMT (Pacifi et al., 1992). There have also been cases of scombroid poisoning where drugs were clearly implicated as contributing factors (Uragoda and Kottegoda, 1977; Senanayake and Vyravanathan, 1981; Chin et al., 1989; Stratton and Taylor, 1991b).

#### 4. Postulated mechanisms of toxicity in scombroid poisoning

In attempting to explain this dose-response anomaly, any hypothesis for the scombroid poisoning mechanism must be consistent with the previously discussed observations regarding what is known about this intoxication, such as response to antihistamine therapy by victims, presence of the toxicity only in decomposed fish, the presence of histamine and metabolites in the urine of victims, and finally, implication of fish species rich in free histidine.

Potential of histamine toxicity by other compounds present in toxic fish has been suggested by a number of investigators (Bjeldanes et al., 1978; Paik and Bjeldanes, 1979; Taylor and Lieber, 1979; Chu and Bjeldanes, 1981; Lyons et al., 1983; Taylor, 1986; Stratton and Taylor, 1991) and requires the presence of dietary histamine. A “barrier disruption” mechanism for potentiation has been suggested in which protective binding of histamine to intestinal mucin is disrupted by potentiators (Parrot and Nicot, 1966). Experiments have demonstrated increased transport of histamine across the guinea pig gut in the presence of cadaverine (Paik and Bjeldanes, 1979; Chu and Bjeldanes, 1981) however experimental evidence that this mechanism plays a major role in scombroid poisoning is not convincing (Taylor, 1986; Mitchell, 1993).

Three additional toxicity mechanisms for scombroid poisoning are examined below, including i) Inhibition-potentiation of histamine toxicity by toxic inhibitors of histamine metabolizing enzymes, ii) mast-cell degranulation to release endogenous but sequestered histamine in the human body, and iii) undiscovered histamine receptor agonists. Discussion of these mechanisms is then followed with an examination of the established condition of histamine intolerance, to address differences in histamine susceptibility in the human population. The presence of dietary histamine in the toxic fish is required in some of the hypotheses and not in others, while it does not conflict with any of them.

##### 4.1. Inhibition-potentiation

DAO and HNMT metabolism of histamine in scombroid poisoning victims plays a central role in the inhibition-potentiation hypothesis. In this suggested mechanism, histamine toxicity is potentiated by the action of DAO and HNMT inhibitors occurring together with dietary histamine in the ingested fish (Taylor and Lieber, 1979; Lyons et al., 1983; Hui and Taylor, 1985). Inhibition of HNMT and DAO leads to increased histamine absorption in the gut and also prevents histamine metabolism in extra-intestinal tissues (Hui and Taylor, 1985). The most frequently cited variations of this hypothesis (Taylor and Lieber, 1979; Lyons et al., 1983) assign the inhibition and potentiation to the fish spoilage-

implicated biogenic amines, putrescine (butane-1,4-diamine) and cadaverine (1,5-pentanediamine). Early evidence for the potentiation of histamine by putrescine and cadaverine was observed in experiments observing guinea pig ileum contraction and DAO inhibition (Mongar, 1957). Among the 38 fish-associated compounds tested by Taylor and Lieber (1979) for DAO inhibition, cadaverine was among the most potent. Cadaverine is plentiful in toxic fish (Arnold and Brown, 1978) and occurs in low levels in non-toxic fish (Meitz and Karmas, 1978). Cadaverine is produced from lysine by bacterial lysine decarboxylase or LDC (Gale and Epps, 1944) in decomposed fish (Taylor and Sumner, 1986). In mahi-mahi, the LDC activity levels have been found to be higher than for HDC (Frank et al., 1985), and strong cadaverine-producing (LDC) activity was also found in the bacterium (*Stenotrophomonas maltophilia*) isolated from fresh and frozen albacore (Ben-Gigery et al., 1999). Lysine is also abundant in many fish including those implicated in scombroid poisoning (Suyama and Yoshizawa, 1973; Perez-Martin et al., 1988; Ruiz-Capillas and Moral, 2004).

Although the above discussion appears to support a likely role for cadaverine in the potentiation of histamine toxicity by DAO inhibition, Hui and Taylor (1985) found that, in studies of the urinary excretion of histamine and its metabolites, cadaverine was a weak inhibitor, being only effective at concentrations 4–5 times that of histamine. Further, Paik and Bjeldanes (1979) found that cadaverine had only a minor impact on histamine metabolism in the guinea pig gut. Studies of scombroid poisoning outbreaks also do not appear to support cadaverine inhibition-potentiation, with conclusions that the very low levels of cadaverine and other biogenic amines detected could contribute little to histamine potentiation (Clifford et al., 1991; Emborg et al., 2006; Emborg and Dalgaard, 2006). Histamine and cadaverine produced in mackerel are the only exception found in the literature, with cadaverine levels exceeding histamine levels by 2–5 times (Klausen and Lund, 1986). With this one exception then, synergism by cadaverine or putrescine alone in scombroid poisoning is not supported by the available literature. On the other hand, as Lehane and Olley (2000) point out and Hui and Taylor (1985) tested in a limited study, the additive effect of a mixture of multiple inhibitors could be enough to be histamine potentiating. Other inhibitors of DAO found in fish include tryptamine, beta-phenylethylamine (Stratton et al., 1991), thiamine and the dipeptides anserine (N-beta-Alanyl-1-methylhistidine) and carnosine (N-beta-alonylhistidine) (Taylor, 1986; Taylor et al., 1989). Anserine is an especially interesting candidate for further study since it is found in swordfish and salmon at much higher levels than histidine (Lukton and Olcott, 1958; Suzuki et al., 1987; Ogata and Murai, 1994) and in yellowfin tuna and albacore tuna at levels comparable to histidine (Arnold and Brown, 1978). Thus there are many other DAO inhibitors known and, given the complexities of living systems and all the possible bacterial products, it is unlikely that all of the important fish-borne DAO inhibitors have been discovered. When inhibition of DAO was directly detected in outbreak-associated fish samples, the results suggested that unknown and potent DAO inhibitors may be found in scombrotic fish

(Hungerford and Arefyev, 1992). Expanded studies using large panels of outbreak-implicated samples and negative control samples are needed to pursue the existence of unknown inhibitors of DAO and HNMT and their possible role in scombroid poisoning.

#### 4.2. Mast cell degranulator

It has been suggested that there may be a “scombrototoxin” that is a mast cell degranulator associated with the spoiled fish (Olley, 1972; Clifford et al., 1991; Ijomah et al., 1991, 1992), which differs significantly from the inhibition-potential hypothesis, in that dietary histamine in the implicated fish is not required. Instead, the observed toxicity is due to release of histamine which is always present in the body, although sequestered with heparin in mast cells. This would satisfy the observed dose-response anomalies. It has been suggested (Lehane and Olley, 2000) that *cis*-urocanic acid (*cis*-3-(3H-imidazol-4-yl)prop-2-enoic acid) might be involved in scombroid poisoning since it is known to be a mast cell degranulator (Wille et al., 1999) and further, has been studied as an indicator for decomposition (Baranowski, 1985). *Cis*-urocanic acid is readily produced by the action of histamine deaminase on free histidine (Shibatani et al., 1974) to produce *trans*-urocanic acid, which could be subsequently photoisomerized to form the *cis*-isomer (Hanson and Simon, 1998). The histidine origin of *cis*-urocanic acid satisfies the requirement that the candidate scombrototoxin be associated with fish high in histidine, but its significance in scombroid poisoning remains unproven. Again, as with the inhibition-potential hypothesis, there is no reason to assume that the degranulating agent is a known compound. Whatever the proposed degranulator, the degranulation hypothesis remains unproven and has been dismissed by some investigators (Morrow et al., 1991; Sanchez-Guerrero et al., 1997) based on the absence (Morrow et al., 1991) of PG-DM(9  $\alpha$ , 11  $\beta$ -dihydroxy-15-oxo-2,3,18,19-tetranorprost-5-ene-1,20-dioic acid, an indicator of Prostaglandin D2 release) and also the absence (Sanchez-Guerrero et al., 1997) of tryptase activity, both well-known indicators of mast cell degranulation (Schwartz et al., 1987). The existence of (non-allergenic) mast cell degranulators in many foods, including fish, has also been claimed by Steinhoff et al. (2004). As pointed out by Ortolani and Pastorello (2006) there is no evidence showing that such compounds can invoke symptoms in humans. Only for citrus fruits, and only *in-vitro*, has the existence of food-borne degranulators been demonstrated (Zeitzi, 1991; Beyer et al., 1994) and an *in-vivo* study using human volunteers, in which a non-allergic food sensitivity to oranges was observed, ruled out mast cell degranulation as the mechanism (Brockow et al., 2003).

#### 4.3. Other histamine receptor agonists

Just as there are inhibitors as yet undiscovered there could also be other histamine receptor agonists in decomposed fish. Although not previously suggested, this is yet another possible explanation for the dose/response anomalies of scombroid poisoning, that the severity of the

response is due to an increase of total histamine-like bioactivity. There is some precedence for this idea, since there is already one example of a free histidine-derived agonist active at one of the other histaminergic receptors. Gizzerocine is a small peptide (Okazaki et al., 1983) found in poor quality feed produced by overheating decomposed fish material. It is a potent H2 histamine receptor agonist, 200 $\times$  more potent than histamine itself (Masamura et al., 1985) and kills poultry by causing excessive excretion of digestive acids. Although certainly not implicated in scombroid poisoning, gizzerocine provides an excellent example of a previously unknown and histidine-derived agonist active at a histamine receptor. Based on this precedent there may be other histidine-derived compounds in scombroid poisoning-implicated fish that could bind to histaminergic receptors, and thus it is not possible to rule out the existence of other agonists without comparing the total histamine receptor bioactivity with the predicted activity based on known histamine concentrations in outbreak-implicated sample extracts. If there were other histaminergic receptor agonists for the various histaminergic receptors with activity comparable to that shown by gizzerocine for H2 receptors, low levels of bioactive compounds could be enough to cause illness. The application of activity-based assays, with observable end points triggered by receptor binding, would thus be very useful.

A potentially powerful approach to exploring the possible mechanisms of scombroid poisoning and for discovering histaminergic bioactives would be a combination of LC-MS and an activity-based assay to screen for “scombrototoxins” in outbreak-implicated fish samples. Indeed, one of the first methods officially approved for the detection of histamine was a biological method (AOAC, 1954) based on the contraction of guinea pig ileum. This assay is actually responding to H1-agonist activity and this approach could be updated and extended by developing cell lines rich in the relevant histaminergic receptors. Transfected cells could be used for this purpose since the H1 receptor has been cloned (Fujimoto et al., 1993) as have the H2 (Gantz et al., 1991), H3 (Lovenberg et al., 1999) and H4 (Liu et al., 2001) receptors. The viability of cell assays in the study of other seafood toxins in samples from outbreak-implicated sample extracts has been demonstrated (Manger et al., 1995) and proved especially powerful when combined with analysis of individual LC-MS fractions (Dickey et al., 1999; Dickey, 2008); combined activity and structure information were easily obtained, even for toxins and toxin metabolites for which no purified standards were available. A similar approach to studying scombroid poisoning is much needed.

Any one of the above hypothesized explanations may apply to some cases of scombroid poisoning and not to others, since scombroid poisoning describes a collection of symptoms and circumstances and thus may not have a single specific mechanism of toxicity.

#### 4.4. Histamine intolerance

Histamine Intolerance is a condition which describes high sensitivity to dietary histamine including histamine-rich foods and wines (Maintz and Novak, 2007) and may

explain the variations between individuals in their susceptibility to dietary histamine in decomposed fish (Motil and Scrimshaw, 1979). Histamine intolerance is a well established condition (Maintz and Novak, 2007), is not a mechanism of scombroid poisoning per se, and does not invoke the presence of other toxic decomposition products or other components unique to fish. Victims may respond to histamine alone, and in one such study, oral administration of 75 mg of histamine (a dose the authors stated is found in normal meals) provoked symptoms in 50% of the test subjects, all of whom were healthy females who had no history of food intolerance (Wöhrl et al., 2004). It is believed that, in histamine intolerance, dietary histamine cannot be scavenged effectively by diamine oxidase (DAO) due to reduced activity of this enzyme in impacted individuals. Determination of DAO activity in patient serum (Mayer et al., 2005) has diagnostic value for histamine intolerance (Missbichle, 2004).

Histamine intolerance is a metabolic disorder, arising from disequilibrium of accumulated histamine and the capacity for histamine metabolism, mainly due to genetically reduced DAO as with known single-nucleotide polymorphisms (SNPs) of the gene coding for DAO in food allergies (Petersen et al., 2003) and other inflammatory and neoplastic gastrointestinal diseases (Petersen et al., 2002). Intestinal DAO may play a prominent role in the differences in degree of histamine intolerance (and thus susceptibility to scombroid poisoning) among the human population, since there is a subpopulation of individuals with a genetic predisposition to gastrointestinal diseases with SNPs of the gene coding for DAO in the gut (Schwelberger, 2004).

In studies of histamine intolerance and hypothesized mechanisms of scombroid poisoning, several variables should be considered in volunteer studies and outbreak studies. Lehane and Olley (2000) pointed out that complicating variables in studies of scombroid poisoning can include consumer misdiagnosis, innate individual variation, body weight, gender differences in metabolism, concomitant medication, and idiosyncratic intolerance, as well as the presence of true allergy.

Some studies may have given biased results due to gender. For example, the relatively high, 50% rate of response to histamine in the study by Wöhrl et al. (2004) may be explained in part by the fact that all 10 volunteers were female. Similarly, in the study by van Geldren et al. (1992) both of the two (of 8) volunteers responding to 70 mg histamine were females and both had plasma histamine levels no higher than the (males) not showing symptoms. Further complicating the gender variable, estrogen can influence histamine action (Kalogeromitros et al., 1995).

As Lehane and Olley (2000) have also pointed out, several variables in the composition of fish samples, fresh or decomposed, can also complicate studies of scombroid outbreaks volunteer trials, and when histamine is administered in volunteer studies in the absence of fish, this should also be done considering other possible interactions. For example, the use of grapefruit juice as a vehicle for administering histamine in studies of scombroid poisoning (Motil and Scrimshaw, 1979) may influence the results since furanocoumarins found in grapefruit juice are

known to inhibit CYP3A, a widely occurring form of the CYP450 family of metabolic enzymes (Guo et al., 2000). Inhibition of these crucial enzymes could lead to metabolic alterations (Maintz and Novak, 2007).

## 5. Bacterial origins of histamine in fish

Histamine is produced from free histidine due to the action of bacterial histamine decarboxylase (HDC) following time-temperature abuse. Although scombroid poisoning is defined as an illness associated with spoiled fish (López-Sabater et al., 1994a; Satomi et al., 1997; Kim et al., 1999, 2000, 2001) and fish products (Kimura et al., 2001; Kung et al., 2009) histamine and other biogenic amines are also found in other foods and also in beverages. Histidine is a common amino acid and so histamine is also produced by bacterial decarboxylation in many other foods and beverages such as wine (Coton et al., 1998) cheese (Sumner et al., 1990), and fermented meat (Roig-Sagués et al., 1997). However, histamine in fermented products, such as wine (Lonvaud-Funel and Joyeux, 1994) cheese (Stratton et al., 1991a; Leuschner et al., 1998) and fish sauce (Satomi et al., 1997; Kimura et al., 2001) is produced by gram-positive lactic acid bacteria while histamine formed in raw fish products is produced primarily by gram-negative enteric bacteria (López-Sabater et al., 1994b; López-Sabater et al., 1996; Gingerich et al., 1999; Kim et al., 2001a,b). There are also differences between the type of HDC involved depending on these two sources. Two distinct classes of HDC enzymes exist, the gram-positive bacteria produce heterometric HDC that contains an activity-critical pyruvoyl group (van Poelje and Snell, 1990; Konagaya et al., 2002) while the HDC of animals and gram-negative bacteria are dependent on pyridoxal 5-phosphate (Kamath et al., 1991). It is also possible that products such as fermented fish sauce could contain histamine from each of the two types of HDC, first from gram-negative bacteria due to decomposition of the source fish prior to sauce production and also histamine from the Gram-positive form of HDC produced during the fermentation step.

Although histamine formation is best controlled by preventing time-temperature abuse, it is now known that there are bacteria with the ability to form elevated concentrations of histamine at temperatures as low as 0–5 °C (Kanki et al., 2004; Emborg et al., 2006). Thus, mesophilic bacteria such as *Clostridium perfringens*, *Morganella morganii*, *Hafnia alvei* and *Raoultella planticola* are not, as previously thought, the only significant producers of histamine in scombroid poisoning. Emborg et al. (2006) identified *Morganella psychrotolerans*, a strong histamine former, as a novel psychrotolerant bacterium, and a 2004 study of *Photobacterium phosphoreum* (Kanki et al., 2004) revealed that these low temperature-adapted bacteria could play a role in scombroid poisoning.

Rapid identification of histamine forming bacteria is an approach useful in managing scombroid poisoning, particularly if post-harvest contamination is taken to be a significant factor in management. Takahashi et al. (2003) describe cloning of HDC-producing genes of several species of gram-negative bacteria. They used an amplification product of the HDC genes to develop a rapid PCR method

which also included simultaneous differentiation by single-strand conformation polymorphism (SSCP) analysis. In their work, 37 strains of histamine-producing bacteria could be successfully detected (from 29 fish isolates and 8 reference strains from culture collections) while 470 strains of non-histamine producers yielded no amplification products. Previous attempts to develop molecular methods were centered on cloning only the pyruvyl-dependant HDC associated with gram-positive bacteria (Jeune et al., 1995).

## 6. Bacterial histidine decarboxylase as an “independent producer” of histamine

Whether produced by gram-positive or gram-negative bacteria, HDC can be present in fish, and histamine can be produced, even when the HDC positive bacteria are no longer viable. This has now been confirmed in experiments using recombinant HDCs of the histamine-producing bacteria *P. phosphoreum*, *Photobacterium damsela*, *R. planticola*, and *M. morgani* in which the bacteria themselves were absent (Kanki et al., 2007). These authors studied HDC activities from these sources as a function of pH, salinity, and temperature as well as the various HDC stabilities in Saury, tuna, and reaction buffer as a function of temperature. The HDC from *P. damsela* was a particularly vigorous producer. Specifically, the conclusion was that HDC is stable in fish meat and is implicated as an independent cause of scombroid poisoning in frozen-thawed fish. Kanki et al. (2007) further speculated from their results that when HDC is implicated as an independent cause of HFP in frozen-thawed fish, the most likely causative agent is HDC of *P. damsela*. There is also anecdotal evidence for active HDC in thawed frozen fish samples analyzed in FDA laboratories. It has been found that on thawing frozen fish composite, samples testing positive for histamine (including samples implicated in scombroid poisoning outbreaks), histamine levels can increase from initial analytical results by much as 100%. These increases are presumably due to increased activity of HDC as frozen composites are thawed to ambient laboratory temperatures prior to analysis. The nature of the problem is further suggested by a successful solution. In the author's laboratory it has been found that freezing (for later analysis) small subsamples of the original composite allow rapid thawing and re-freezing and stable histamine levels. Cooking destroys HDC activity so the above changes are not observed in cooked fish, but histamine itself is a relatively stable compound, even in processed seafoods. Histamine is not destroyed by freezing or heating such as normal cooking, hot smoking or canning (Arnold and Brown, 1978; Taylor, 1986; Lehane and Olley, 2000; Flick et al., 2001; FDA/CFSAN, 2001; Kim et al., 2003).

## 7. Histamine levels used in regulation

Histamine levels are targeted in regulatory efforts to address the threat of scombroid poisoning (FDA/CFSAN, 2001; EU 2005). Although, as discussed above and in other reviews (Taylor et al., 1989; Lehane and Olley, 2000; Dalgaard et al., 2008; Al Bulushi et al., 2009) scombroid

poisoning is not simple histamine poisoning, currently available information suggests that scombroid poisoning is nonetheless caused primarily by histamine in seafood (Dalgaard et al., 2008) and that reducing histamine formation in seafood should be the main objective in control efforts. A useful and practical aspect of the European Union regulations is that they specify fish species associated with a high amount of histidine (EU, 2005). These same regulations also stipulate that the critical levels of histamine are different according to whether the products have undergone enzyme maturation treatment in brine or not. For the enzyme matured products, the critical concentration of histamine is 200 mg/kg, and for simple fish products is 100 mg/kg, based on the average of nine samples. Of the nine samples no two can be higher than 100 mg/kg (and 200 mg/kg) levels but none can be higher than 200 mg/kg (or 400 mg/kg for enzyme matured products). In the US (FDA/CFSAN, 2001) a more conservative defect action level at 50 mg/kg is used. In principle, fresh fish meat contains no histamine; in practice however, acceptable product may contain traces of histamine at levels much lower than the 50 mg/kg action levels used in the US (FDA/CFSAN, 2001) or the 100–200 mg/kg action levels used in Europe (EU 2005). Finally, most scombroid poisoning-implicated fish species share the common trait of having high levels (often over 1000 mg/kg) of free histidine (Takagi et al., 1969, Suyama and Yoshizawa, 1973).

Although other biogenic amines such as cadaverine and putrescine have been indicated as potential health risks (Shalaby, 1996; Önal, 2007; Al Bulushi et al., 2009) and it has been suggested that the levels of these two polyamines need to be considered in any histamine toxicity assessment (Al Bulushi et al., 2009), action levels have been established only for histamine in regulations targeting scombroid poisoning. Even as indicators of decomposition, recent studies by Emborg and Dalgaard (2007) have cast further doubt on the value on these and other alternative biogenic amine levels for managing scombroid poisoning-implicated species, since linear relationships were found between histamine levels and biogenic amine levels and the actual levels of cadaverine and putrescine were often very low.

## 8. Impact of scombroid poisoning and management of susceptible fish

Since it is strictly the result of fish product mishandling, scombroid poisoning can be prevented. It is nonetheless a persistent and global problem (Lehane and Olley, 2000; Dalgaard et al., 2008). Data for worldwide outbreaks of scombroid poisoning were updated recently in project results (BIOCOM, Biogenic amines in seafoods – assessment and management of consumer exposure studies) reported by Dalgaard et al. (2008). Together with ciguatera, scombroid poisoning continues to account for the majority of finfish-borne illness (Dalgaard et al., 2008). Not only does it rank among the most prominent seafood intoxications, Dalgaard et al. (2008) recently reported that scombroid poisoning accounted for 38% of all seafood associated outbreaks in the United States and in England and Wales for 32% in the 1990s. Rates of seafood consumption did not correlate with outbreak rate. Further, for the countries with

the highest (reported) outbreak rates, the numbers ranged from 2 to 5 outbreaks/year/million people (examples are Denmark, New Zealand, France and Finland). The US was a notable exception, where in Hawaii a much higher outbreak rate of 31/year/million people was reported (CSPI, 2005).

It has also been asserted (Dalgaard et al., 2008) that it has not been possible to reduce the occurrence of scombroid poisoning either in Europe or the USA. Recreational catches likely play a major role in both this perception and also the high numbers of outbreaks reported in Hawaii, however the authors (Dalgaard et al., 2008) do not further delineate the outbreaks into those associated with recreational or commercial catches, restaurants, etc. The importance of recreational catches versus commercial harvests is also alluded to by Lehane and Olley (2000) who point out that in developed countries such as the US and Japan most outbreaks of scombroid poisoning result from consumption of fish caught recreationally. As Lehane and Olley (2000) further elaborate, temperature abuse may occur on recreational boats that lack adequate refrigeration. In 1991 a National Academy of Science report (NAS, 1991) reported that more than 20% of all fish sold in the United States are caught by sport fishers, and Gellert et al. (1992) asserted that sale of recreationally caught fish posed a risk of scombroid poisoning while the commercial fish industry was responsible for few cases of scombroid poisoning. The authors emphasized that recreationally caught fish may pass from noncommercial and recreational boats directly to markets, restaurants, and distributors without being subject to the regulations imposed on the commercial fishing industry. Hawaii is a very popular recreational fishing location and thus this may account for the high outbreak rate observed there. Finally, the globalization of seafood in the last decade has greatly amplified all food safety challenges, leading to huge increases in international trade including seafood; among these products are the already popular scombroid species such as tuna (Constance and Bonanno, 2009). It is fortunate that improvements in seafood safety and quality are helping to offset the threat. One review suggests (Lehane and Olley, 2000) that these improvements can be traced to the application of risk analysis, establishment of international standards, and use of risk analysis plus hazard analysis and critical control point (HACCP) principles.

HACCP is a preventative strategy for managing seafood safety in the US that is centered on the identification of key physical, chemical, and biological hazards, rather than finished product inspection. Briefly, critical control points (CCP's) are identified. These are critical points for product safety along every aspect of handling from harvest to the consumer. For fish susceptible to scombroid poisoning, time and temperature specifications define the CCP's along with avoiding contamination (FDA/CFSAN, 2001). The seafood HACCP program in the US has continued to evolve. Readers can gain greater knowledge of HACCP from training courses and from online resources of the Seafood Network Information Center (<http://seafood.ucdavis.edu>). An emphasis on scombroid poisoning in US HACCP efforts is reflected in a 2005 evaluation of seafood HACCP in which the USFDA calls for further safety improvements by

processors of scombrototoxin-forming fish species (FDA, 2005). Globalization of the food supply is being addressed in multiple countries via harmonization of food standards (Caswell and Hooker, 1996), HACCP is now applied in many other countries besides the US (Unnevehr and Jensen, 1999) and has attained the status of an international food standard (Caswell and Hooker, 1996). In the US, the surge of food imports resulting from globalization of trade, including seafood imports, is being addressed by opening FDA offices in many regions of the world and pursuing new import and food protection plans (Bristol, 2008).

At the laboratory and method development level, further steps can be taken to strengthen HACCP efforts to reduce scombroid poisoning. New, effective tools for HACCP could include a dependable field testing method simple enough for on-board, dockside, and inspectional use. Such tools must also be combined with modern and efficient methods for laboratory use, for screening and also for reference methods to verify results.

## 9. Laboratory methods for histamine and related biogenic amines in fish and fish products

The number and variety of methods developed for laboratory histamine testing of fish and fish products is impressive. In contrast to many of the other more potent seafood toxins, the relatively high action levels established for histamine in fish allow for the detection of histamine using a variety of different approaches ranging from simple and inexpensive thin layer chromatography (TLC) procedures to resource-intensive and more powerful LC-MS methods.

Most of the separation methods applied to histamine in fish and fish products use reversed-phase high performance liquid chromatography (HPLC) with detection schemes based on pre-column derivatization (Hui and Taylor, 1983; Meitz and Karmas, 1978; Petridis and Steinhart, 1995; Malle et al., 1996; Hwang et al., 1997) or post-column derivatization (Veciana-Nogues et al., 1995; Glória et al., 1999; Brillantes and Samosorn, 2001) to produce fluorescent products or strong chromophores, but direct UV detection of histamine's imidazole ring has also been applied (Frattini and Lionetti, 1998; Shakila et al., 2001, Cinquina et al., 2004b). Other popular separation-based methods include ion chromatography (Cinquina et al., 2004a), capillary electrophoresis (Gallardo et al., 1997; Zhang and Sun, 2004), paper electrophoresis (Sato et al., 2002, 2006), thin layer chromatography (Lieber and Taylor, 1978; Bajc and Gačnik, 2009) and gas chromatography-mass spectrometry (Marks and Anderson, 2006).

Liquid chromatography with mass spectrometric detection (LC-MS) has also been applied to the detection of histamine (plus multiple biogenic amines) with some novel pre-column derivatization schemes (Song et al., 2004; Bomke et al., 2009) and without derivatization, ion chromatography-MS has also been applied (El Aribi et al., 2006). Most recently, high-speed separations have been achieved using new stationary phases suited for hydrophilic interaction liquid chromatography (Quilliam et al., 2009). Generally Liquid Chromatography-Mass Spectrometry (LC-MS) of histamine and other biogenic amines in fish does not

enjoy the same widespread application as in marine toxins research, presumably because less expensive instrumentation is sufficient.

With a few exceptions, many of the published HPLC methods for detecting histamine perform adequately. What are missing are rigorous validation studies to firmly establish them as reference methods. Although an HPLC method based on pre-column dansylation (Malle et al., 1996) has been stipulated as the reference method of choice by the European Commission (Commission Regulation, 2005) this method has been validated only internally (Duflos et al., 1999). Reference methods should be proven thoroughly in inter-laboratory studies in which multiple labs demonstrate that the method is rugged. The most widely used and officially accepted method to detect histamine in fish is a batch fluorescence method (AOAC, 1977). Although it is time consuming, requires manual manipulations and timing and ion exchange cleanup, Codex Alimentarius (<http://www.codexalimentarius.net>) recommends this method as a reference method, and for the validation of other methods (AOAC, 1977). In addition to AOAC Int. and Codex Alimentarius, other international groups, such as the European Standardization Committee (CEN) (<http://www.cen.eu/cenorm/homepage.htm>) set standards for official methods.

Due to the effort and investment required in official validation studies, particularly the inter-laboratory studies required for official reference methods, it is advisable that methods be evaluated by regulatory stakeholders and researchers. Starting in 2004, an international group (Hungerford, 2005) has pursued AOAC Int. validation of modern methods for seafood toxins. Methods and protocols for their evaluation are examined by regulatory and industry stakeholders, analytical chemists, toxicologists, and others ([http://www.aoac.org/marine\\_toxins/voting.htm](http://www.aoac.org/marine_toxins/voting.htm)) taking into account sample matrix considerations and criteria ([http://www.aoac.org/marine\\_toxins/analyt\\_criteria.htm](http://www.aoac.org/marine_toxins/analyt_criteria.htm)) for performance and practicality. Many of the voting group members are also active in CEN and Codex Alimentarius, which helps to maintain continuity.

Specific method protocols and validation study data are then reviewed by the voting members of the group and AOAC Int. methods committees ([www.aoac.org](http://www.aoac.org)). Participation in the group is not restricted to voting members, and discussions and information sharing takes place within a much larger community [http://www.aoac.org/marine\\_toxins/roster.htm](http://www.aoac.org/marine_toxins/roster.htm) electronically, at annual meetings, and in workshops.

### 9.1. Laboratory-screening methods for histamine in fish and fish products

In addition to reference methods there is a need for methods well suited to high-speed screening. Generally these methods detect histamine without employing separations, and laboratory-screening methods for histamine in fish have been applied for years in industry and/or regulatory labs but few have been officially validated beyond the level of single laboratory (within-laboratory) validations.

The most rapid method for detecting histamine is based on flow injection analysis (FIA) and is capable of screening

60 sample extracts per hour (Hungerford et al., 1990). It is based on flow-based automation and kinetics optimization of the same (*o*-phthalaldehyde condensation) chemistry used in the reference method (AOAC, 1977). Concerns about control of reaction conditions and flow rates (Rogers and Staruszkiewicz, 2000) have already been addressed by the method's adaptation for "turn-key" commercial instrumentation (Hungerford et al., 2001). When combined with an (immobilized) DAO reactor, a modified version of this FIA procedure is capable of high-speed and simultaneous screening for both histamine and the assay of overall DAO inhibition in fish extracts (Hungerford and Arefyev, 1992).

Enzymatic methods are attractive for their selectivity, and flow injection has been used in combination with enzyme electrodes for easy automation (Takagi and Shikata, 2004; Watanabe et al., 2007). Other types of enzyme-linked assays have also been developed. An enzyme sensor array based on DAO employs a multivariate approach to take into account the reactivity of DAO for diamines including histamine, putrescine and cadaverine (Lange and Wittmann, 2002) and another enzyme sensor used histamine oxidase to detect histamine via oxygen consumption (Ohashi et al., 2006). An enzyme based kit for histamine in fish has been commercialized. The kit is based on recombinant histamine dehydrogenase (Bakke et al., 2005) and is available in microplate format as BioScientific's MaxSignal®.

Many other commercial test kits are available, based on selective antibodies (Lehane and Olley, 2000; Staruszkiewicz and Rogers, 2001; Emborg and Dalgaard, 2007; Tom, 2007; Köse et al., 2009). These include enzyme-linked immunosorbent (ELISAs) assays in quantitative formats such as Neogen's Veratox, the Food EIA® by Labor Diagnostika Nord (LDN), Ridascreen® and Ridaquick® both by R-Biopharm, the Biomedix Histameter®, the Beckman-Coulter Histamarine®, and the semi-quantitative Transia Tube® Histamine by Raisio Diagnostics. Some ELISAs are also available in a simpler and more rapid qualitative format, in which a positive result is obtained only at a threshold histamine level. These include Neogen's Alert®, the Biomedix Histameter®, Transia Tube® Histamine by Raisio Diagnostics. The first dipstick format (qualitative) test is available from LDN. This kit, called Histasure®, is based on fluorescence and lateral flow. Two kits, both of them quantitative ELISA kits, have been validated. Beckman Coulter's Histamarine® (developed and submitted for validation by Immunotech) was independently tested by the AOAC Research Institute (<http://www.aoac.org/testkits/testkits.html>) and found to detect the presence of histamine in fresh tuna, canned tuna and fresh mahi-mahi ([www.beckmancoulter.com/CustomerSupport/IFU/ivdd/IM2369.pdf](http://www.beckmancoulter.com/CustomerSupport/IFU/ivdd/IM2369.pdf)) and the Veratox® assay of Neogen Corp. has been performance tested and certified by the AOAC Research Institute for application to fresh, canned or pouched tuna in oil or water (AOAC, 2007). Several test kits have been evaluated for application to fresh, naturally contaminated, and histamine-spiked canned and fresh tuna and mahi-mahi (Rogers and Staruszkiewicz, 2000; Staruszkiewicz and Rogers, 2001). The kits investigated included Histaquant®, Veratox®, Alert®, and Histamarine® and also included three kits no longer available. The batch fluorescence, Codex-recognized official method (AOAC,



1977) served as a reference method in these studies. It was found that all of the kits were portable and able to discriminate pass (<50 mg/kg histamine) and fail samples (50 mg/kg or more histamine). Regarding their ease of use, it was observed that the kits tested were convenient but still required some training.

More recently, studies have been conducted to evaluate the performance of many of the currently available histamine test kits for their application to heavily salted or fermented seafood products (Köse et al., 2007, 2009). The performance of the kits for testing these ethnic seafood products (also termed traditional fish products, or TFP in the European Union) was evaluated using the EU-approved (Commission Regulation, 2005) HPLC method (Malle et al., 1996) as reference. Among the quantitative kits, the LDN Food EIA<sup>®</sup> test kit performed well for determining histamine in TFPs, the Veratox<sup>®</sup> kit gave good recoveries but showed some deviations from the HPLC results, and the Histaquant<sup>®</sup> kit was unable to accurately quantitate histamine in TFPs. For qualitative screening, the Histasure<sup>®</sup> and Transia Tube<sup>®</sup> kits both performed well.

Growing interest in portable format histamine test kits, both qualitative and quantitative, is clear from the popularity of workshops and training courses addressing them (Hungerford, 2008b, 2009) indicating that more of the commercial test kits should be validated.

## 9.2. Field testing for histamine in fish and fish products

Although the potential value of “dockside” or on-board testing to HACCP-based seafood safety cannot be overstated, the development of practical field testing schemes, with rapid and simplified overall analytical procedures has proved elusive, even though many screening methods including test kits have been developed. First, although some existing screening methods might be adapted, the procedures must be even further simplified and still be fast and rugged. As Lehane and Olley (2000) pointed out, test kits must also be affordable. Even if all these requirements are met, significant barriers to the success of any field testing are posed by on-site challenges of sampling, extraction, and general sample handling. In traditional (and currently predominant) laboratory methods, the samples are first selected, transported to the lab, thawed, trimmed, divided, homogenized, etc. These operations are much more time consuming than the determination step itself and sample accountability procedures also add to the delays. Further, a large quantity of fish must be removed and homogenized.

In 1997 the author presented and published a scheme for rapid, on-site removal of gram quantities of frozen fish particles without thawing the entire fish, and also without the need for additional grinding (Hungerford et al., 1997). Intended for rapid screening to reveal toxic fish, this approach does not attempt collection of a representative sample. A small sample is withdrawn from the anterior, ventral area, a location known to show the highest levels of histamine (Frank et al., 1981; Hungerford, 2008a). Sample removal is based on the observation that drilling into frozen fish brings up particles. Removal of the fish sample is easily accomplished using a cordless electric drill in

conjunction with a tapered plastic centrifuge tube. The tube has been modified to have a hole drilled at the tapered end that is the same diameter as the drill bit. By holding the tapered end flush with the fish surface, drilling into frozen fish results in partially frozen particles being trapped in the tapered end. The volume, and thus weight of the frozen fish is set by the drill diameter and penetration depth. With this arrangement about 2 g of frozen meat, in particle form, can be gathered in less than a minute with about 3 penetrations and approximately 10% relative precision. A particularly key advantage of this technique is that the resulting particles are fine enough to be used in rapid extraction. In-lab validations and then on-site pilot studies will be required to prove the feasibility and practicality of this approach to field sampling and extraction. Although the original application of this drill sampling procedure was for rapid detection of volatiles, the same approach has been proven feasible for histamine detection by flow injection analysis in studies mapping histamine distribution in mahi-mahi (Hungerford, 2008a, 2008b). The method is clearly extendable to other detection schemes. Field tests based on immunoassay variants, enzymatic tests, or other rapid-response technologies in user friendly formats like LFIC dipsticks, cassettes, or portable instruments could be combined with this or similar novel sampling and extraction schemes.

Histamine is not often grouped together with marine toxins, and it is instructive to compare histamine with these other toxins found in seafood. The ciguatoxins, the tetrodotoxins, and the various shellfish-borne toxins are predominantly microbial in their etiology, with the majority of them being secondary metabolites produced by various microplankton or bacteria. Scombroid poisoning is due to bacterially-derived toxin or combination of toxins, so in this sense it can be classified as a microbial toxin as are the microplankton-derived toxins. On the other hand, differences between scombroid poisoning and other types of seafood poisoning are glaring; in no other seafood intoxication can the sequestered “toxin” be found in healthy individuals never exposed to the vector. Scombroid poisoning is also different from other seafood intoxications in many other respects, ranging from its pharmacology to its unclear pathogenesis and, perhaps most important, its prevention.

Research collaborations between those investigating outbreaks and those in the biomedical research community are needed to prove or disprove the various hypothesized mechanisms for scombroid poisoning.

With every benefit there are always associated risks, and just as the consumption of red meat and poultry involve specific areas of risk, so does eating improperly handled seafood. On the other hand, the threat posed by any of the seafood intoxications must be put into a broader human health context. Seafood from the world’s oceans provide excellent nutrition and enjoy increasing popularity and even medical endorsement. Regular consumption of fish and other seafood in the diet is recommended by many health authorities and by nutritionists worldwide. Specifically, there is motivation to improve cardiovascular health by eating more seafood versus red meat (Narayan et al., 2006). Better understanding of scombroid poisoning and

other types of seafood poisoning will improve seafood safety efforts and will be key to enjoying these benefits.

## 10. Conclusion

Contamination of fish with histamine is due to mis-handling and bacterial production of histamine. Although the role of histamine as a seafood “toxin” in scombroid poisoning is not fully understood, detection of histamine and the enforcement of action levels are useful for control purposes. Hypothesized mechanisms for scombroid poisoning remain unproven, and improved prevention of scombroid poisoning can result from investigations of these mechanisms to gain a better understanding of the origins of scombroid poisoning. Many methods for detecting histamine have been described. However, refinement and international validation of laboratory and field testing methods should be pursued to improve the protection of public health amidst globalization of the seafood supply.

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## Conflict of interest

None.

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