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Histamine and Scombrottoxins

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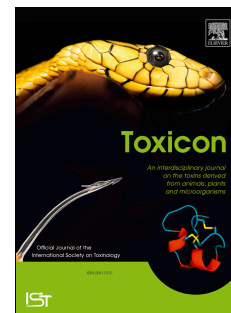
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Histamine and Scombrottoxins

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Abstract

Histamine intoxications result when histamine-metabolizing enzymes are compromised or overwhelmed by dietary histamine in the human body. This can occur either due to metabolic enzyme deficiencies, such as in histamine intolerance to wines, aged cheese and other foods or from high concentrations of histamine following ingestion of decomposed fish. The presence of histamine in decomposed fish and fish products results from bacterial decarboxylation of free L-histidine following product mishandling. Consequently, histamine intoxications from mishandled fish, commonly referred to as scombrototoxin fish poisoning (SFP) or scombroid poisoning, require high levels of free L-histidine only found in certain species of pelagic fish. Differential diagnosis is required of clinicians since dietary histamine intoxications produce the same symptoms typical of release of endogenous histamine due to IgE-mediated seafood allergies or anisakiasis. Although high levels of dietary histamine are responsible for SFP, histamine has important physiological functions and tends to exert toxic effects only at doses beyond the physiological range. Endogenous histamine is essential to local immune responses, regulation of gastric acid secretion in the gut, and neurotransmission in the central nervous system. Scombrototoxins, postulated to explain histamine's augmented toxicity in scombrototoxic fish, are a milieu of histamine and other bioactives. Since time-and-temperature abuse is required to produce high levels of histamine in fish, management consists of ensuring proper handling by identifying hazards and critical control points (HACCP) and maintaining a "cold chain" from catch to consumption. Reference methods for detecting histamine have received increased attention and the European Commission has validated a popular precolumn dansylation-based HPLC method

through inter-laboratory collaboration and studied method equivalence with the AOAC fluorescence method 977.13 recognized by Codex Alimentarius. Much progress has been made during the last decade in the development and validation of rapid screening methods for detecting histamine in food and especially in fish products. These include many innovative sensors and several validated commercial test kits, many of them based on a recombinant form of the enzyme histamine dehydrogenase (HD).

Keywords: histamine poisoning; scombrototoxin fish poisoning; scombroid poisoning; histamine; seafood safety; scombrototoxicosis; histamine test kits

1. Introduction

Scombrototoxin fish poisoning (SFP) also known as scombroid poisoning, scombrototoxicosis, or histamine fish poisoning, results from consuming dark-muscled fish that has been mishandled. Histamine is generated in putrefied fish when inadequate chilling of raw dark-muscled fish allows bacterial, enzymatic conversion of free L-histidine (Hungerford, 2010, Feng et al., 2016). SFP is allergy-like both in its symptoms and treatment (Prester 2016) with H1R antagonists (diphenhydramine or chlorpheniramine) or H2R antagonists (cimetidine) often prescribed (Guss, 1998).

Scombrototoxin fish poisoning is named for the first fish species recognized as playing a role in scombrototoxicosis, members of the histidine-rich family Scombridae (Suyama and Yoshizawa, 1973; Perez-Martin et al., 1988; Ruiz-Capillas and Moral, 2004) such as tuna and mackerel, among others. These are dark-muscled fish, and like all fish commonly implicated in scombrototoxin fish poisoning, they are rapid-swimming and migratory pelagic fish, sharing a common need for buffering of accumulated acid in their muscles. This requirement is generally filled in dark-muscled fish by the essential amino acid, L-histidine but in some fish by certain dipeptides (Boldyrev and Severin, 1990, Abe, 2000). There are many other dark-muscled fish implicated in SFP which contain high levels of free L-histidine. Fish species of the families *Clupeidae* (herrings, sardines, shad), *Coryphaenidae* (mahi-mahi), *Engraulidae* (anchovies), *Pomatomidae* (bluefish), *Scombridae* (mackerels, tunas, bonito) and *Scomberesocidae* (sauries) are identified as scombrototoxin hazards by Codex Alimentarius and the European Union (FAO, 2013). In their systematic study, Columbo et al (2018) also identified *Istiophoridae* (marlin), *Xiphiidae* (swordfish) as well as the species *Chanos chanos* (milkfish), and *Arripus trutta*

(Australian salmon, not a salmonid). Although it has paradoxically white flesh due to the presence of wax esters, escolar (*Lepidocybium flavobrunneum*) is also implicated in SFP and contains high levels of free histidine (FAO, 2013). Although only rarely, salmonids have also been reported in suspected cases of SFP but inclusion of salmonids as potentially scombrototoxic species has been controversial. An FAO/WHO review (WHO 2018) concluded that all available evidence suggests that salmonids “do not pose the same level of risk” of scombrototoxicosis as the other commonly implicated species. Only when the sensory shelf-life was exceeded (from advanced, readily apparent decomposition) did salmonids produce toxic histamine levels (WHO 2018). Salmon products have a very high production volume, trade, and consumption and observations of only a sparse number of intoxications also indicates that they do not pose a significant health risk. In their updated hazards guide (FDA 2020) the US Food and Drug Administration has acknowledged that illnesses associated with the consumption of decomposed salmon have been reported which were attributed to the production of toxins other than histamine such as the biogenic amines putrescine and cadaverine. There is some irony in the fact that although L-histidine is not found in salmon at the high levels typical of other pelagic fish, it was first isolated from salmon protamine by Albrecht Kossel in 1896 (Jones, 1953).

2. Symptoms and Treatment of SFP

Initial symptoms of scombrototoxicosis appear from 10 minutes to one hour following consumption of contaminated fish (Ansdell, 2008). They include facial flushing or

sweating, burning or peppery taste in the mouth, dizziness, nausea, headache, tachycardia, and cold-like symptoms. These can quickly advance to symptoms that are allergy-like, mimicking the pathophysiology of histamine release (Taylor et al, 1989) such as facial rash (urticaria but less commonly wheals) flushing, and generalized edema. There are also the usual gastrointestinal symptoms typical of many types of food poisoning such as short-term diarrhea and abdominal cramps. Severe cases can include blurred vision, respiratory distress, swelling of the tongue. Unlike the potentially fatal anaphylaxis associated with allergies, scombrotxin fish poisoning is generally not directly associated with fatalities (Taylor, 1986; Demoncheaux et al., 2012, Ridolo et al., 2016, Harmelin et al., 2018). Given the role of histamine as a neurotransmitter in the central nervous system (CNS), it is noteworthy that in addition to the common symptoms of headache, nausea, and vomiting (Maintz and Novak, 2007), others such as anxiety are sometimes observed (Russell and Maretic, 1986), that initial symptoms include dizziness and that severe cases can also include blurred vision (Kobza Black, 1998; Specht, 1998).

In some cases, recovery can require days but typically is complete within 24 hours (Taylor, 1986). Those with preexisting conditions can have serious respiratory and cardiac complications but among otherwise healthy individuals these have not been observed (Russell and Maretic, 1986; Taylor et al., 1989; Ascione et al., 1997). Motil and Scrimshaw (1979) reported that there are broad variations in sensitivities by individuals to SFP. Attack rate is a key aspect of the epidemiology and an important clue to support differential diagnosis versus seafood allergy; Most individuals eating the same meal will respond to scombrotic fish while only a few individuals will become ill if the illness

observed is due to allergies (Taylor et al., 1989). Differential diagnosis should also take into account anisakiasis or IgE-mediated reactions to *Anisakid* larvae (Feng et al., 2016). Medical histories are critically important to rule out allergies and in their absence the presence of histamine in the patient's plasma or in the implicated meal remnants are very important to avoid misreporting of SFP cases as allergies. The Centers for Disease Control have emphasized that SFP is underreported (Pennotti et al., 2013) particularly small outbreaks. Treatment of SFP is primarily supportive and antihistamines are usually administered (Lerke et al., 1978, Blakesley, 1983, Guss, 1998). Although it does not rule out allergies, response to antihistamines by victims of SFP supports a role for histamine in this intoxication (Taylor et al., 1989).

3. Role of Histamine in Human Physiology

A disparity exists in the dose-response relationship in which oral administration of pure histamine does not produce the same result as similar histamine levels ingested via decomposed fish: Scombrototoxic fish are much more toxic than an equivalent dose of pure histamine, as pointed out by Taylor et al. (1984) and Taylor (1986). The conclusion has been (Taylor et al., 1989; Lehane and Olley, 2000, Hungerford, 2010) that "histamine poisoning" does not adequately describe the nuances of scombrototoxic fish poisoning. Enhancement of histamine toxicity by other components of the spoiled fish reinforces the concept of "scombrototoxins" the compounds which, including histamine, are postulated to cause scombrototoxicosis.

Although histamine is the primary agent involved in scombrototoxin fish poisoning (Barrett et al., 2017, Hungerford, 2010) histamine is not a toxin and is a vital messenger molecule with wide-ranging roles in mammalian physiology. Endogenous histamine is found throughout the body and is released from enterochromaffin-like cells, mast cells, and neurons (Katzung, 2007). A wide range of receptors found in the human body (H1R, H2R, H3R and H4R) referred to as histaminergic, are targeted by histamine. Via these receptors endogenous histamine is essential to local immune responses, regulation of gastric acid secretion in the gut, neurotransmission in the central nervous system, regulation of circadian rhythm, body temperature, food intake, learning and memory, and immune response (Ohtsu 2010; Smolinska et al., 2014). Histamine is also vital in mediating intestinal ischemia (Kalchmair et al., 2003) mucus secretion, immunomodulation, vascular permeability, hematopoiesis, wound healing, and the day-night rhythm. Histamine is also known to influence the induction of cell proliferation and angiogenesis by other polyamines in tumors (Kusche et al., 1980, Raithel et al., 1998).

The essential role of histamine in human health is underscored by a variety of health problems besides scombrototoxicosis, including the familiar role in allergies (Germundson, et al., 2020) but also histamine intolerance (Prester, 2016, Maintz and Novak, 2007), anxiety and obsessive-compulsive behaviors (Zhang et al., 2020), Parkinson's disease (Fang et al., 2020) and a variety of other maladies. Histamine also impacts mediation of the potentially fatal pulmonary cytokine storms associated with pathogenic viruses such as COVID-19 (Eldanasory, 2020). The term "histaminergic" describes anything in mammalian systems which liberates histamine or is activated by it. The histaminergic system refers to the complex system within the human body

mediated by histamine. A central component of the histaminergic system, histamine receptors are a class of G protein-coupled receptors which bind histamine as their primary ligand (Hill et al., 1997). G protein-coupled receptors, including the histamine receptors, are trans-membrane proteins which are cell surface receptors found only in eukaryotes and which are involved in many diseases (Trzaskowski et al., 2012).

Many of the toxic effects of dietary histamine in scombrototoxicosis and their resulting symptoms are related to the normal physiological roles of endogenous histamine: Headache, flushing, and hypotension results from dilation of peripheral blood vessels, painful itching associated with the rash are due to stimulation of motor and sensory neurons, symptoms involving the gastrointestinal tract such as diarrhea, abdominal cramps, nausea, and vomiting result from smooth muscle contraction, palpitations and tachycardia are caused by stimulation of the heart by histamine to increase its contractility, while urticaria, hemoconcentration, and edema of the eyelids are due to increased capillary permeability (Visciano et al., 2014).

4. Metabolism of Dietary Histamine in SFP and Histamine Intolerance

Understanding histamine metabolism in the human body is critical to understanding the fate of ingested histamine including hypothesized mechanisms of the SFP and other maladies such as histamine intolerance (Maintz and Novak, 2007, Wantke, 2015). In humans it is diamine oxidase (DAO) and histamine N-methyl transferase (HNMT) which are the enzymes metabolizing histamine (Brown et al., 1959; Bieganski et al., 1980; Bieganski et al., 1983; Maintz and Novak, 2007, Peralta et al., 2020). Although HNMT is

localized in the cytosol of cells (Brown et al., 1959), DAO is excreted directly into the circulation (Schwelberger et al., 1998, Peralta et al., 2020) and so DAO plays the major role in histamine catabolism (Bieganski et al., 1980; Bieganski et al., 1983) scavenging extracellular histamine which has implications for both SFP (Hungerford, 2010) and histamine intolerance (Maintz and Novak, 2007, Peralta et al., 2020) following ingestion of histamine-rich food. Some drugs such as chloroquine, clavulanic acid, cimetidine, verapamil, isoniazid, metamizole and amitripyline inhibit DAO (Sattler et al., 1985; Sattler et al., 1990; Wantke et al., 1998, Leitner et al., 2014) resulting in serious consequences including cases of SFP where drugs were clearly implicated as contributing factors (Uragoda et al., 1977; Senanayake et al., 1981; Chin et al., 1989; Stratton et al., 1991b).

High sensitivity to histamine may explain some of the observed variations between individuals in their susceptibility to SFP in decomposed fish (Motil and Scrimshaw, 1979) and also describes a condition known as histamine intolerance, a condition which applies to other histamine-containing foods and beverage most notably aged cheeses, beer, and wine (Maintz and Novak, 2007, Peralta et al., 2020). Histamine intolerance does not require the presence of other components of fish or toxic decomposition products. In contrast to SFP, victims may respond to histamine alone including oral administration of just 75 mg of histamine, an amount typical of normal meals (Wöhrle et al., 2004). Determination of DAO activity in patient serum (Mayer et al., 2005, Peralta et al., 2020) has diagnostic value for histamine intolerance (Missbichle, 2004, Manzotti et al., 2016, Peralta et al., 2020). It is believed that ineffective scavenging of dietary histamine by DAO is to blame for histamine intolerance due to reduced activity of this

enzyme in susceptible individuals. Single-nucleotide polymorphisms (SNPs) of the gene coding for DAO occur resulting in reduced DAO levels and increases in food allergies (Maintz et al., 2011) and other inflammatory and neoplastic gastrointestinal diseases (Petersen et al., 2002). Schwelberger (2004) found a subpopulation of individuals with a genetic predisposition to gastrointestinal diseases with SNPs of the gene coding for DAO in the gut, and so intestinal DAO may be responsible for both differences in degree of histamine intolerance and susceptibility to SFP. Intestinal DAO is produced by enterocytes in the intestinal mucosa, and DAO is the first barrier to dietary histamine in the human body (Wantke, 2015).

5. Postulated Scombrottoxins and Mechanisms of SFP

Theories on the true nature of SFP differ as to which compounds, in addition to histamine, participate in producing the mechanism(s) of this disease as well as the observed dose-response disparities. FDA states that although the terms “histamine poisoning” and “histamine fish poisoning” are often used rather than SFP, the association of other compounds with the illness presents difficulties with these terms (FDA 2020). Consistent with their postulated roles with histamine in SFP, these compounds will be referred to here as scombrottoxins. With the exception of mast cell degranulation, all of these theories require that histamine be present and so only in the mast cell activation theory is histamine not included with the other scombrottoxins. Although none of the theories of scombrototoxicosis have been proven since these theories were reviewed (Lehane and Olley, 2000, Hungerford, 2010), some progress

has been made, and new analytical tools developed to explore them. From a mechanistic view, the postulated categories of scombrottoxins can be delineated as either intestinal barrier disruptors, inhibitors of diamine oxidase (DAO), mast cell degranulators, or other histaminergic receptor agonists of unknown identity (Hungerford, 2010). Some of the suggested scombrottoxins, most notably the many biogenic amines as well as *cis*-urocanic acid (*cis*-UCA) also have significant direct toxicity even in the absence of histamine.

5.1 Biogenic Amines and other Inhibitors of DAO in Inhibition-Potentiation

An often-cited theory postulated for the mechanism of SFP, inhibition-potentiation of histamine toxicity, invokes inhibition of DAO and HNMT by inhibitors of these metabolic enzymes (Taylor and Lieber, 1979; Lyons et al., 1983; Hui and Taylor, 1985). Just as reductions in DAO due to polymorphisms (Maintz et al., 2011) lead to histamine intolerance (Maintz and Novak, 2007) inhibition of DAO is postulated to lead to SFP. Since intestinal DAO is the first barrier to ingested histamine (Wantke, 2015) inhibition of DAO leads to increased histamine absorption in the gut. Since DAO is also excreted directly into the circulatory system (Schwelberger et al., 1998, Peralta et al., 2020) the same mechanism could prevent histamine metabolism in extra-intestinal tissues (Hui and Taylor, 1985). Potentiation of histamine by compounds known to occur in spoiled fish was first observed in studies of the contraction of guinea pig ileum (Mongar, 1957) observing the effect of putrescine and cadaverine in the presence of histamine. These results led Taylor and Lieber (1979) to test a panel of 38 fish-associated compounds for DAO inhibition. Cadaverine, which is abundant in scombrottoxic fish (Arnold and Brown, 1978), was among the most potent. Cadaverine is an especially promising candidate,

being produced from lysine by bacterial lysine decarboxylase or LDC (Gale and Epps, 1944) in decomposed fish (Taylor and Sumner, 1986) and present at high levels in mahi-mahi (Frank et al.,1985), in the bacterium *Stenotrophomonas maltophilia* found in albacore (Ben-Gigery et al.,1999). Finally, the enzyme substrate and cadaverine precursor lysine is also abundant in many fish (Suyama and Yoshizawa,1973; Perez-Martin et al.,1988; Ruiz-Capillas and Morál, 2004).

All these observations encourage the idea that cadaverine is a likely “scombrototoxin” by virtue of inhibition of DAO and potentiation of histamine toxicity. Experiments by Hui and Taylor (1985) appear to contradict this assertion. Examining urinary excretion of histamine and its metabolites they found that cadaverine was not a strong inhibitor of DAO requiring high cadaverine concentrations (4-5 times that of histamine) to be effective. Studies by Paik and Bjeldanes (1979) using guinea pig gut also do not lend support to cadaverine as a potent inhibitor of DAO since only a minor impact was found on histamine metabolism. Finally, studies of SFP outbreaks (Clifford et al.,1991, Emborg et al., 2006; Emborg and Dalgaard, 2006) also do not support a role for cadaverine inhibiting DAO with only very low levels of cadaverine and other biogenic amines detected relative to histamine. Histamine production in mackerel may provide the only support so far since in a study by Klausen and Lund (1986) mackerel cadaverine could exceed histamine levels by 2-5 times. Finally, it is important to emphasize that in decomposed fish it is feasible that a milieu of multiple inhibitors could be present and produce enough inhibition of DAO to potentiate histamine in SFP (Lehane and Olley, 2000). There is some experimental evidence for this in a limited study by Hui and Taylor (1985). Familiarity with cadaverine and putrescine as

decomposition indicators, in addition to the early experiments of Mongar (1957) led to a focus on biogenic amines as likely candidates in potentiating the toxicity of histamine (Bjeldanes et al., 1978; Taylor and Lieber, 1979; Taylor et al., 1984; Hui and Taylor, 1985; Taylor, 1986). Other compounds should be further studied as potential scombrottoxins inhibiting DAO, such as beta-phenylethylamine and tryptamine (Stratton et al., 1991), thiamine, and the dipeptides anserine (N-beta-alanyl-1-methylhistidine) and carnosine (N-beta-alanylhistidine) studied by Taylor (1986) and Taylor et al.(1989). Studies by Vinagre et al. (2011) and Taoka et al. (2019) have shown that anserine is found in abundance in other pelagic fish such as coho salmon (*Oncorhynchus kisutch*) and in fish sauce prepared from Giant Masu Salmon (*Oncorhynchus masou*). Among these candidates, only beta-phenylethylamine and tryptamine are decomposition products. There is no requirement that all inhibitors impacting DAO be the result of decomposition. Another consideration is that not all the inhibitors of DAO occurring in fish have been discovered. In one limited study in which outbreak samples from mahi-mahi were directly tested for DAO inhibition using flow injection analysis (Hungerford and Arefyev, 1992) potent inhibition was observed relative to putrescine, cadaverine, and negative controls while anserine showed significant inhibition.

5.2 Scombrottoxins as Intestinal Barrier Disruptors

Another mechanism suggested for potentiation of histamine toxicity in SFP is known as barrier disruption, which again focuses on the protective role (Turner, 2009, Peterson and Artis, 2014, Wantke, 2015) of the intestine. Early studies looking at disruption of the intestine and its potential role in SFP were focused on protective binding of histamine to intestinal mucin (Chu and Bjeldanes, 1981) which is disrupted by potentiators (Parrot

and Nicot,1966). Although Paik and Bjeldanes (1979) and Jung and Bjeldanes (1979) found increased transport of histamine across the mammalian gut in the presence of cadaverine there has not been acceptance of this mechanism playing a major role in SFP (Taylor,1986; Mitchell,1993, Lehane and Olly, 2000). Although not focused on mechanisms of SFP, a new study by Grosheva et al. (2020) looked at rapid screening for host and microbiota regulators of intestinal barrier function and may offer some clues regarding other mechanisms for potentiation of histamine toxicity. In the intestine, adjacent epithelia form tight junctions (TJs). These structures are an essential part of the physical barrier regulating movement of solutes, ions, and water across the intestinal epithelium (Peterson et al., 2014). After screening a large panel of potential disruptors, Grosheva et al. (2020) found that putrescine and histamine caused damage to the TJs of intestinal cells. The study included cultured cells, tissues, and mice. Of all the compounds studied, putrescine had the most disruptive effect, greatly increasing permeability.

Until recently our knowledge of the toxicity of biogenic amines other than histamine has been scarce (Ladero et al., 2010). This includes two of the most familiar biogenic amines, putrescine and cadaverine. Animal studies by Til et al. (1997) revealed their relatively low toxicities in studies using Wistar rats, where no adverse effects were observed for either biogenic amine up to 2000 mg/kg. Perhaps this rather low toxicity encouraged the idea that these biogenic amines can only contribute to HFP by indirect mechanisms such as their impact on histamine metabolism (inhibition-potentiation).

Thanks to a series of cytotoxicity studies using cultured intestinal cells our knowledge of biogenic amines toxicity has expanded greatly. Starting with histamine and tyramine

327 Lineras et al.(2016) employed an in-vitro model using cultured human intestinal
328 epithelium cells to observe cytotoxicity of several biogenic amines. The studies used
329 real-time cell analysis (RTCA) of HT29 intestinal cell cultures. In this in-vitro model,
330 tyramine was found to be about ten times more cytotoxic than histamine, with an IC_{50} of
331 3.2 mM for tyramine versus an IC_{50} of 26.0 mM for histamine following 24-hour
332 exposure. Tyramine also acted more rapidly and caused death by necrosis while
333 histamine caused death by apoptosis (Linerar et al., 2016). Apoptosis is a
334 “programmed” form of cell death (Kanduc et al., 2002) triggered by many biochemical
335 signals of which histamine is one (Toninello et al., 2004). The cytotoxicity threshold of
336 4.0 mM determined by Lineras et al., 2016) for histamine corresponds to 440 mg/kg
337 which supports previous assumptions by Taylor (1985) and by Shukla et al. (2011) who
338 suggested that concentrations of histamine greater than 400 mg/kg and 500 mg/kg,
339 respectively, are likely dangerous to human health. No legal limit has been set for
340 tyramine in fish or any food (European Food Safety Authority (EFSA) 2011). The
341 cytotoxicity threshold of 2.2 mM found by Linares et al. (2016) corresponds to 302
342 mg/kg, a level far lower than 2529 mg/kg, the highest concentration of tyramine found in
343 cheese (EFSA, 2011). Recently Del Rio et al. (2019) applied the HT29 intestinal cell
344 model system and RTCA (HT29/RTCA) approach of Lineras et al. (2016) to study the
345 in-vitro toxicity of cadaverine and putrescine. They found that both of these biogenic
346 amines were cytotoxic at levels found in foods commonly rich in biogenic amines. The
347 IC_{50} determined for putrescine was 39.8 mM while cadaverine yielded an IC_{50} of 40.7
348 mM. Determining the dose-response relationship is fundamental in risk assessment
349 studies of bioactives such as drugs under development and also toxins in food

(Faustman and Omen, 2001). In these studies two key indicators focus on the toxicity threshold of the curve, including the highest concentration at which no toxicity is observed (non-observed adverse effect level or NOAEL) and also the lowest concentration where toxicity is detected (lowest observed adverse effect level, or LOAEL). In their study Del Rio et al. (2019) reported NOAEL and LOAEL values for putrescine at 5 mM and 10 mM, respectively while for cadaverine they were 2.5 mM and 5 mM, respectively. Using the NOAEL values, the corresponding levels for cadaverine and putrescine are 441 mg/kg and 255 mg/kg respectively.

Between these two studies (Linerias et al., 2016, and Del Rio et al., 2019) these groups found that tyramine is by far the most cytotoxic of the biogenic amines followed by histamine and then cadaverine, with putrescine the least cytotoxic. Of these four biogenic amines, only histamine caused apoptosis, while the other three caused death by necrosis.

Synergy has been detected between tyramine and histamine. Del Rio et al. (2017) found that histamine has a synergistic effect on the cytotoxicity of tyramine on intestinal cell cultures, even at levels of histamine below the legal (EU) limit for scombroid fish (Del Rio et al., 2017). At concentrations corresponding to 190 mg/kg histamine and 500 mg/kg tyramine, the IC_{50} values for tyramine were decreased more than 2-fold by the presence of histamine. The molecular mechanism causing the synergy has not been elucidated (Del Rio et al., 2017). At the time of writing, no similar studies using the intestinal cell model have been reported investigating synergies between histamine, cadaverine, and putrescine.

In contrast to conclusions reached for the above compounds, spermine and spermidine, although found to be cytotoxic towards the same (HT29/RTCA) approach first described by Linares et al. (2016), were not sufficiently cytotoxic at levels found in foods commonly rich in biogenic amines to be deemed a health risk (Del Rio, 2018). The lowest concentration of spermine found to be cytotoxic for the intestinal cell cultures had an of LOAEL = 3.23 mM, equivalent to 654 mg/kg while for spermidine cytotoxic effects in the intestinal cell cultures yielded LOAEL = 10 mM, equivalent to 1452.50 mg/kg. Tryptamine and β -phenylethylamine are biogenic amines associated with causing hypertension (Ladero et al., 2010). Tryptamine can occur at concentrations as high as 2280 mg/kg in fish sauces and at 362 mg/kg in other fish products. In contrast β -phenylethylamine has been at detected at 172 mg/kg in fish sauces, 18 mg/kg in fermented fish and 180 mg/kg in other fish products (EFSA, 2011). Again, using the HT29/RTCA approach Del Rio et al. (2020) found that both tryptamine and β -phenylethylamine were cytotoxic with both of these biogenic amines causing cell death via necrosis and apoptosis. Further, β -phenylethylamine produced a LOAEL of 1.86 mM, equivalent to 225 mg/kg, while tryptamine had a LOAEL of 0.5 mM, equivalent to 80 mg/kg. They concluded (Del Rio et al., 2020) that only tryptamine posed a significant health risk, since it was cytotoxic at levels less than the concentrations seen in fermented food, in contrast to β -phenylethylamine.

Considering these data additional studies of the toxicity of biogenic amines and of the (intestinal) barrier disruption model seem warranted. This need is given even more impetus by new text included in the FDA Fish and Fishery Products Hazard Guide (FDA 2000) which states that “Decomposition can result in the production of other toxins (e.g.,

biogenic amines, such as putrescine and cadaverine) that have the potential to cause illness, even in the absence of histamine formation.”

5.3 Scombrottoxins as Mast Cell Degranulators

Interest in *cis*-UCA as a potential scombrotxin has been spurred by the role postulated by Lehane and Olley (2000) in histamine poisoning and reviewed by others (Hungerford, 2010). It was suggested that degranulation of mast cells could cause release of endogenous histamine versus a dietary role for histamine. One reason for interest in the mast cell degranulation theory (Clifford et al., 1991; Ijomah et al., 1991) are occasional reports of symptoms resembling SFP following consumption of non-scombroid fish (Bartholomew et al., 1987). Since these fish contain only low levels of histamine it was reasoned that release of endogenous histamine was responsible. Most information in the literature regarding *cis*-UCA are centered on the human health impact of *cis*-UCA for its role in immunosuppression and skin cancer (Bernard et al., 2019). Urocanic acid is produced by bacterial enzymatic deamination of L-histidine as *trans*-urocanic acid which can then be photo-isomerized to the biologically active *cis* isomer (Bernard et al., 2019). Pursuing the mast cell degranulation postulate of Lehane and Olley (2000), the laboratory of Zare et al (2012) developed an HPLC method for detecting *cis*- and *trans*-urocanic acid in fish based on ion pairing and UV detection. Zhong et al. (2018) subsequently developed an HPLC method based on reactive extraction cleanup and chaotropic chromatography. Zare and colleagues used their method to study the production of urocanic acids in Indian mackerel (Zare et al., 2013), tuna (Zare et al., 2015a), and other selected fish and fish products (Zare et al., 2015b). They found that at warm temperatures typical of histamine production although urocanic

acids increase at first in Indian mackerel, they then decrease (Zare et al., 2013). In cold storage, urocanic acids steadily increase with time. An important requirement of all the theories of scombrototoxicosis is that there is consistency between what is known of the proposed scombrototoxin and the microbiology involved in producing the potential scombrototoxins implicated in the illness. Little is known about the microbiology of urocanic acids production in scombroid fish. Zhong et al. (2019) studied production of urocanic acids by *Acinebacter* in chub mackerel and found that urocanic acids were a primary metabolite. They found that urocanic acids were produced during exponential growth, however on entering stationary phase the bacterium used up preformed urocanic acids rapidly as a response to starvation. The same pattern had been observed previously in a culture of *Pseudomonas fluorescens* (Imanaka, 1962). These findings can explain observations by Zare et al. (2013) that during storage of Indian Mackerel, urocanic acids can either increase or decrease, or first increase and then decrease. Zhong et al (2019) state that the Zare et al. (2013) observations can be explained by the changing nutrition or physiology of the bacteria, resulting in formation or degradation of urocanic acids. The proposed role of *cis*-UCA as a scombrototoxin does fit what we know of the importance of L-histidine (since urocanic acid is the product of L-histidine deamination in fish) and the role of bacteria found in fish (in this case bacterial histidine deaminase). *Cis*-UCA does not directly degranulate mammalian mast cells: Neuropeptides degranulate the mast cells after *cis*-UCA binds to the peripheral terminals of unmyelinated primary sensory nerves, leading to production of the degranulating neuropeptides (Scarchio et al., 2012). Although this does not eliminate *cis*-UCA as a potential scombrototoxin, it does complicate the theory. Generally, attempts

to prove the mast cell degranulation theory have been discouraging. Morrow et al (1991) and Sanchez-Guerrero et al (1997) failed to detect serum tryptase after volunteers were given marlin with high levels of histamine, a marker of mast cell degranulation and secretion. Further, a study that included 10 patients with SFP revealed serum tryptase levels in the normal range while 50 patients with an established allergic disorder had increased tryptase levels (Ricci et al., 2010). A report by FAO/WHO on SFP (FAO 2013) concluded that available data did not support the mast cell degranulation theory.

5.4 Unknown Histamine Receptor Agonists.

Previously Hungerford (2010) postulated that unknown histamine receptor agonists besides histamine may occur in decomposed fish. These undiscovered scombrotoxins could be yet another possible explanation for the anomalies observed for histamine dose/response in SFP. Clues to structural requirements for histamine receptor agonists come from gizzerosine (Okazaki et al., 1983), a small peptide which is derived from poor quality feed. Decomposed fish material used in the feed produces gizzerosine during processing. This small molecule appears to be derived from histamine and is named for its biological activity, erosion of gizzards in poultry by virtue of being a potent H₂ histamine receptor (H₂R) agonist. Masamura et al. (1985) found that gizzerosine is 200X more potent than histamine itself and causes excessive excretion of digestive acids. Gizzerosine has structural similarity to both histamine and lysine. Drugs developed as histaminergic receptor modulators may also provide some direction in

looking for other scombrottoxins active at histaminergic receptors. Of note are
impromidine (Durant et al., 1978) and betazole (2-(1H-pyrazol-5-yl)ethanamine)
described by Hammond et al. (1978). Both are H₂R agonists. Another compound,
betahistine (2-[2-(methylamino)ethyl]pyridine) is paradoxically a weak H₂R agonist and
strong H₃R antagonist (Botta et al., 2001). In this case the H₃R receptor antagonist
activity is most important since it increases the levels of several neurotransmitters,
including histamine, acetylcholine, norepinephrine, serotonin, and GABA released from
the nerve endings. Structural similarities between these bioactive compounds and
histamine [2-(1H-Imidazol-4-yl)ethanamine] include include the ethanamine group
(histamine and betazole) and above all imidazole (impromidine, histamine, gizzerosine).
Betazole is also isobaric with histamine with the atoms of the imidazole group of
histamine rearranged into pyrazol. As stated previously (Hungerford 2010) combining
an activity-based assay to screen for “scombrottoxins” in outbreak-implicated fish
samples with LC-MS/MS would be a powerful approach to exploring the possible
mechanisms of scombroid poisoning including histaminergic bioactives.

6. Bacterial Origins of Histamine in Fish

Following time-temperature abuse, histamine is produced from free histidine due to the
action of bacterial histamine decarboxylase (HDC). Maintaining the cold chain is
critical in preventing histamine formation. Mesophilic bacteria such as *Clostridium*
perfringens, *Morganella morganii*, *Hafnia alvei*, *Raoultella planticola* have traditionally
received the most attention in studies of bacterial histamine production in SFP. It is now
recognized that mesophiles are not the only significant producers of histamine in fish.
Emborg et al (2006) identified *Morganella psychrotolerans*, a novel psychrotolerant

bacterium (Wang et al., 2020) and strong histamine former, 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. Psychrotrophic bacteria have been discovered which form histamine at temperatures as low as 0-5 °C (Kanki et al., 2004; Emborg et al. 2006, Bjornsdottir-Butler et al., 2016, Bjornsdottir-Butler et al., 2018, Wang et al., 2020). These findings illuminate a need to determine how formation of histamine by these psychrotrophs relate to regulatory limits and sensory evaluation of product quality (Bjornsdottir-Butler et al., 2016). *Photobacterium* species are psychrotrophic bacteria found in fish and the marine environment, one species of which has been implicated in an outbreak of SFP (Emborg and Dalgaard, 2006). Five species of *Photobacterium* are known to be strong producers of histamine, including *P. angustum*, *P. aquimaris*, *P. damsela*, *P. kishitani*, and *P. phosphoreum* (Bjornsdottir-Butler et al., 2018). Although especially well adapted to cold temperatures, *Photobacterium* spp are sensitive to elevated temperatures (Kumar et al., 2000).

Two distinct classes of bacterial HDCs exist and evolved independently (Snell and Recsei, 1981). One type of HDC found in Gram-negative bacteria and animals is dependent on pyridoxal-5-phosphate (PLP) while the other occurs in Gram-positive bacteria and fermented products such as fish sauce, cheese, beer and wine and contains an activity-critical pyruvoyl group. (Landete et al., 2008). In their efforts to identify the mechanism of histamine production in *Photobacterium phosphoreum*, Bjornsdottir-Butler et al (2020) found and characterized a novel *hdc2* gene which produced a new type of histidine decarboxylase, HDC2. The histidine decarboxylase (HDC) activity of the protein was comparable to pyridoxal-5-phosphate (PLP) dependent

HDC from *P. kishitanii* and *M. morganii*. Stable at low temperatures and sensitive to elevated temperatures, the enzyme showed optimum activity between 20 and 35 °C and pH 4.0 and was not sensitive to salinity. Bjornsdottir-Butler et al (2020) suggested that further characterization of the enzyme may help in developing control measures to minimize histamine production.

Relevant to both control measures and fish sample handling, even if HDC-producing bacteria present in susceptible fish are no longer viable, preformed HDC may be able to produce additional histamine during thawing of frozen samples. Indirect evidence for this is found in a study using recombinant HDC to study histamine production in the absence of the bacteria (Kanki et al., 2007) and anecdotally in thawing fish tissue composites for analysis (Hungerford, 2010) where increases in histamine during sample handling are sometimes observed. These changes are not observed in cooked fish since heating destroys HDC activity. On the other hand, histamine itself is a relatively stable compound and 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; FDA, 2020).

6.1 Detection of Histamine Producing Bacteria in Fish

Due to the central role of histamine producing bacteria, methods for their identification, particularly methods based on the polymerase chain reaction (PCR) are useful in managing scombroid poisoning. Takahashi et al (2003) described cloning of HDC-producing genes of several species of gram-negative bacteria. Using an amplification product of the HDC genes their (conventional) PCR method also included simultaneous

differentiation by single-strand conformation polymorphism (SSCP). Previous attempts (Jeune et al., 1995) to develop molecular methods were centered on cloning only the pyruvoyl-dependent HDC associated with gram-positive bacteria. Sabry et al (2019) applied (conventional) PCR using the *hdc* gene to study occurrence of histamine producing bacteria in retail sardine and mackerel in Egypt. Since Takahashi's experiments with *hdc*-dependent conventional PCR, the subsequent development of quantitative PCR (qPCR) aroused great interest in food microbiology and food safety (Hanna et al., 2005, Martínez et al., 2011) and qPCR was soon applied to detecting histamine producing bacteria. Bjornsdottir-Butler (2011) described the first qPCR method for detecting Gram-negative bacteria producing histamine in fish. Mace et al. (2013) combined a propidium monoazide step with qPCR to quantify viable *Photobacterium phosphoreum* in salmon steaks. Wongsariya et al (2015) developed qPCR methodology targeting the *hdc* gene in *M. morganii*, *E. aerogenes*, and *A. baumannii*. They found that the primers could detect *M. morganii*, *E. aerogenes* before the histamine level reached 50mg/kg. In addition to PCR technologies, rapid sequencing has also been applied to the detection of histamine-producing bacteria in fish (Peters et al., 2021).

7. Histamine Levels Used in Regulation and Control

To assess the mean concentration of histamine in fish causing histamine poisonings, Columbo et al (2017) conducted a systematic review and meta-analysis of histamine poisonings. Approximately 1100 mg/kg caused scombroid poisoning but with a wide range in uncertainty, from 423-2,900 mg/kg. Mclauchlin et al (2006) stated that

histamine intoxication can occur at levels of about 1000 mg/kg. FDA has stated that histamine levels in illness-implicated fish have been above 200 mg/kg and often above 500 mg/kg (FDA 2020). This can be compared to the FAO (2013) meeting report which derived a histamine limit of 200 mg/kg based on a NOAEL of 50 mg and 250 g serving size. Histamine intoxications do occur at concentrations lower than 1000 mg/kg, and Shalaby (1996) states that concentrations of 50-200 mg/kg may be toxic. FDA uses a guidance level of 50 mg/kg for histamine in fish. Since histamine has a very heterogeneous distribution within fish and between fish, FDA states that “If 50 mg/kg is found in one section of a fish or lot, there is the possibility that other sections may exceed 500 mg/kg” (FDA, 2020).

In the European Union critical levels for histamine in fish and simple fish products (EU, 2005) target species high in histidine, with emphasis on the families *Engraulidae*, *Clupeidae*, *Coryfenidae*, *Pomatomidae*, *Scombridae*, and *Scombresosidae*. Critical levels for histamine in fish and simple fish products are 100 mg/kg histamine (EU, 2005). These levels are based on the average of nine samples. Of the nine, no more than two can be greater than 100 mg/kg and no sample may have a level above 200 ppm. The EU allows higher critical levels of histamine for “the fishery products which have undergone enzyme maturation treatment in brine and manufactured from fish species associated with a high amount of histidine” (EU, 2013). For these enzyme-maturated (brined, ripened or fermented) products, the critical limit based on the average histamine content is 200 mg/kg or less, and no more than two samples may have levels between 200 mg/kg and 400 mg/kg. No sample can exceed 400 mg/kg. For

fish sauce only one sample is required, with the histamine content not exceeding 400 mg/kg (EU 2013).

8. Impact and Management of SFP

Scombrotoxicosis can be prevented since it is due to time and temperature abuse following harvest. Despite this SFP, along with ciguatera poisoning (WHO, 2020), remains a leading cause of fish-borne illness (Lehane and Olley, 2000, Dalgaard et al, 2008, Hungerford, 2010, Pennotti et al., 2013). In a 2013 report the Centers for Disease Control (CDC) concluded that Scombroid poisonings affected more Americans than reported in surveillance systems. Using extrapolated numbers, they estimated over 35,000 illnesses resulting in 162 hospitalizations between 2000 and 2009 (Pennotti et al., 2013). When preventing time-temperature abuse is a critical aspect of supply chains, as in the control of histamine formation, the term "cold chain" is used.

Mercogliano and Santonicola (2019) described the main factors resulting in histamine production related to the tuna supply chain. All stages including catching, processing, storage, and distribution must be considered in the cold chain since they all impact histamine production. Mercogliano and Santonicola (2019) also suggested that secondary control measures might be developed considering emerging approaches such as irradiation, hydrostatic pressures, active packaging or food additives.

Hazard Analysis Critical Control Point (HACCP) is a science-based system for assuring food safety which requires seafood processors to identify potential food safety hazards and to prevent them from occurring (FDA, 2015). Imported seafood products are also

addressed and written verification procedures are required of importers to assure that imported seafood is processed in a way to meet requirements of FDA Seafood HACCP programs (FDA, 1995). A review of the US Seafood HACCP program for 2006-2014 by the Food and Drug Administration (FDA 2015) concluded that the overall plan and implementation success rates for the control of histamine were high but varied considerably: pathogen growth and toxin formation success rates were 85-89%. The initial HACCP step which consists of identifying plan controls was 95-98% and actual implementation was 91-96%. These compare well with overall rates of plan and implementation for all pathogens of 56-77%. In spite of these encouraging numbers, SFP remains the dominant chemical intoxication in fish and fish products in the US (Dewey-Mattia et al., 2018) and a common cause of food poisoning worldwide (De Cerio et al., 2016). Since the seafood production and distribution system has been increasingly globalized with more than 80% of US seafood is imported, it has become more complicated to protect the public from SFP. (NMFS, 2012).

9. Detection of Histamine in Implicated Fish

The relatively high action levels required to detect histamine in fish have allowed considerable freedom in devising detection strategies. Since we last reviewed histamine detection methodology for analyzing fish (Hungerford, 2010), much progress has been made in the development and validation of detection methods for histamine. Reference methods have also received increased attention, and the European Commission has conducted interlab-validation of their official precolumn dansylation-based HPLC method and studied method equivalence with the AOAC fluorescence method 977.13 recognized by Codex Alimentarius. Advances in rapid screening methods have received

the greatest emphasis including many innovative sensors and new commercial test kits. Rapid test kits for histamine were in the past (Hungerford, 2010) dominated by immunoassays, particularly enzyme-linked immunosorbent assays (ELISAs). Simplified and more portable immunoassays have been developed but recently enzymatic assays have been developed which offer some advantages.

Perhaps the most influential analytical method for detecting histamine in fish, AOAC 977.13 is based on a fluorescence method using condensation of histamine with o-phthalaldehyde (OPA) developed by Shore et al. (1959) to measure histamine in mammalian tissues. The original method used butanol extraction from alkalinized extracts followed by back-extraction to eliminate L-histidine, which they found produced similar excitation and emission spectra to histamine. This procedure removes matrix-derived L-histidine, the major interference with the analysis. In the CODEX-approved fluorescence method (AOAC 977.13) L-histidine, present in high concentrations in the implicated fish, is removed using an anion exchange column under alkaline conditions. A modified version of AOAC 977.13 has been single laboratory validated (Bjornsdottir-Butler et al., 2015). The method uses 96 well-microplates and a fluorescence plate reader to measure the final fluorescence rather than serial readings via conventional cuvette. Extractions are conducted using by cold methanol rather than a lengthy heating and cooling procedure in the original method. The authors claim a 45% increase in throughput, with this increase assuming samples have already been thawed, composited, and aliquoted. Moitessier et al. (2020) described a modified procedure using cold extraction and substituting 4-methoxyphthalaldehyde (MOPA) for OPA. The authors claimed improved performance.

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647 **9.1 Liquid Chromatographic Methods for Histamine and other Biogenic Amines**

648 Interest in detecting other biogenic amines in addition to histamine (Venkateswarlu et
649 al., 2016) continues based on their use as decomposition indicators (Meitz and Karmas,
650 1978), the direct toxicity of these compounds, (Ladero et al., 2009) and the postulated
651 mechanisms for enhancement of histamine toxicity by other biogenic amines (Hui and
652 Taylor, 1985). Many methods have been developed for detecting biogenic amines by
653 HPLC (Önal, 2007, Önal et al., 2013, Biji et al., 2016, Mohammed et al., 2016). Starting
654 among the original literature on SFP, most of the HPLC methods routinely and officially
655 used to detect histamine and other biogenic amines in fish use dansyl chloride for pre-
656 separation derivatization of the amines followed by UV detection (Hui and Taylor, 1983).
657 The evolution of these methods has culminated with a method by Duflos et al. (1999)
658 now officially validated for histamine (Duflos et al., 2019). A variety of HPLC methods
659 closely related to the original (Hui and Taylor, 1983) and Duflos (1999) method have
660 been described over the years including an application by Chen et al (2010) to an SFP
661 outbreak. Most recently the dansyl chloride approach has been adapted to the analysis
662 of dried bonito flakes (Qiao et al., 2020) while Wang et al. (2020) modified the sample
663 handling aspect of the method to use ultrasound-assisted dispersive solid-phase
664 extraction. The dansyl chloride approach has also been applied to a UHPLC method
665 simultaneously detecting 10 major free amino acids in addition to histamine, cadaverine,
666 putrescine, and tyramine in mahi-mahi and yellowfin tuna (Bai et al., 2019). Although
667 not as commonly used as dansyl chloride derivatization, another classic approach for
668 HPLC analysis of biogenic amines is reaction with o-phalaldehyde prior to separation

and fluorescence detection, most recently a method developed by (Kounnoun et al., 2020). A very rapid and economical UHPLC method for detecting histamine alone by UV-diode array, which does not use chemical derivatization and limits the use of organic solvents, has been developed by Cicero et al. (2020).

9.2 Mass Spectrometric Methods for Histamine and other Biogenic Amines in Fish

As with many application areas of analytical chemistry, mass spectrometry-based methods for detecting histamine and other biogenic amines continue to be developed for detection in fish. LC-MS/MS methods for biogenic amines, surprisingly limited in number a decade ago (Hungerford, 2010) have increased in recent years. Considering the capabilities for universal detection, LC-MS/MS methods would seem especially well suited to detecting a full range of biogenic amines since they otherwise require chemical conversion to allow either UV or fluorescence detection. Sagratini et al (2012) described an LC-MS/MS method for detecting histamine and 7 other biogenic amines without derivatization using STRATA X solid phase extraction for sample cleanup. Adequate performance required matrix-matched standards. Self et al (2011) reported an HPLC-Orbitrap method for detecting eight biogenic amines in tuna and later Self and Wu (2012) developed a UHPLC-Orbitrap MS method for detecting histamine and 7 other biogenic amines in seafood products. Both of these studies used extraction by matrix solid-phase dispersion and urocanic acids were also included although the *cis* and *trans* isomers were not separated. Nei et al. (2017) investigated direct analysis of histamine in fish using real time mass spectrometry (DART-MS). They used an internal standard to develop a rapid

screening method. Their study did not include naturally contaminated samples and even with spiked samples matrix effects were observed. Ion chromatography was combined with mass-spectrometric detection by Kočar et al. (2021) to develop a method suitable for the detection of 8 biogenic amines without derivatization or sample cleanup and with recoveries showing no evidence of matrix effects. Tolerance to sample matrix by this method is further supported by its prior application by Ščavničar et al. (2018) to detecting biogenic amines in cheese. To further study the physiology and human health implications of histamine-related illness including scombroid poisoning, the accuracy of methods for detecting histamine metabolites in human fluids following histamine intoxications are crucial. This is examined in detail by Nelis et al. (2020) in their methodology for detecting a variety of human metabolites using LC-MS/MS.

9.3 International Reference Methods for Histamine in Fish

Reference methods are critical to support the development of new methods, to verify the results of rapid screening, and for settling trade disputes. The batch fluorescence method using conventional fluorescence spectrometry and ion exchange cleanup (AOAC 977.13) remains the recognized reference method of Codex Alimentarius.

In Europe the first EC-approved HPLC method for detecting histamine was based on precolumn derivatization with dansyl chloride and internal standard 1,3-diaminopropane (Duflos et al., 1999). Following EC approval of a change in the internal standard from 1,3-diaminopropane to 1,7-diaminoheptane, an interlaboratory study was initiated. The study addressed tuna, herring, and mackerel, and three fish product categories, fish

with enzymatic maturation, fish without enzymatic maturation, and fish sauce. The validation efforts revealed sample matrix issues leading to poor recoveries for some matrices. While performance was excellent with (95%) recoveries for fresh tuna, recoveries for herring and mackerel were low at 36% and 70%. Performance of the method improved considerably (recoveries from herring 78-90%) when matrix matched standards were used and other improvements such as in sample extraction were applied. Following detailed studies and modifications to address sample matrix effects the interlaboratory study was published by Duflos et al. in 2019 and approved as EN ISO 19343. Prior to publication of the validation study, the same method (using the 1,7 diaminoheptane internal standard) was evaluated by Stroka et al. (2014) for equivalence to the Codex approved fluorescence method (AOAC 977.13) and again the same matrix issues were encountered. Stroka et al. (2014) reported that when the EU HPLC method was applied as described in legislation, histamine levels were overestimated by 35% versus the Codex method (Stroka et al., 2014). The internal standard used in the EU HPLC method appears to play an important role in overestimating histamine levels, and when external standards were used the overestimation was only 7%.

9.4 Rapid screening methods for histamine in fish and fish products

In the last decade there has been renewed interest in developing rapid screening methods for detecting histamine in fish (Hungerford and Wu, 2012), including a variety of innovative sensors as well as new commercial test kits, with many of the kits now

validated. Histamine sensors for rapidly testing fish have seen a renaissance with a variety of novel approaches, many of them based on electrochemical sensors. These include flexible printed electrochemical immunosensors based on carbon nanotubes (Shkodra et al., 2020) or graphene (Parate et al., 2020; Nakthong et al., 2020), or sensors using the selectivity of histamine-imprinted polymeric materials (Serrano et al., 2020). Wang et al. (2021) described graphene transistor-based sensor using gold nanoparticles and multi-walled carbon nanotubes. A portable, amperometric immunosensor using Prussian blue-chitosan-gold nanoparticle nanocomposite films was developed by Dong et al. (2017). Other electrochemical sensors use screen-printed electrodes coupled with enzymes to produce disposable biosensors. These include a diamine oxidase-modified sensor reported by Torre et al (2020) and a screen-printed platinum nanoparticle-modified carbon electrode coupled with DAO and MAO (Dalkiran et al., 2020). Fluorescent immunoliposomal nanovesicles have also been used to detect histamine (Bajpai et al., 2020) and both fluorescent and colorimetric detection is accomplished using gold nanoparticles by Bi et al. (2020). Li et al (2019) have developed a colorimetric strip based on self-assembled polydiacetylene vesicles. Another approach to detecting histamine described by Feng et al. (2018) uses the selectivity of molecular imprinted polymers (MIPs) in which histamine-specific nanoparticle MIPs are immobilized to microplates to capture histamine. O-phthalaldehyde (OPA) labeling of the captured histamine then allows detection fluorometrically within the microwells. Surface-enhanced Raman spectrometry (SERS) is the detection principle used in a $\text{Fe}_3\text{O}_4/\text{Au}@ \text{ATP}@ \text{Ag}$ nanorod sandwich structure developed by Li et al (2019). Aptamer-based sensors have also been developed for detecting histamine in fish, including a gold nanoparticle aptamer assay

(Lerga et al., 2020). For some sensor designs and detection principles, inherent limitations must be considered: Sensors using DAO must overcome specificity limitations since they will respond to multiple biogenic amines, and with all aptamer-based systems, the presence of RNAase in samples is a potential problem.

Enzyme linked immunosorbent (ELISAs) assays in quantitative formats have been previously reviewed (Hungerford, 2010) and are still widely used for rapid screening in field laboratory settings. A controlled laboratory environment is required for ELISA since as mentioned in previous work (Hungerford and Wu, 2012, Hungerford et al., 201) although ELISA offers high sensitivity and speed, ELISA methods require careful control of timing-and temperature.

In efforts to develop faster, simplified and more field-friendly kits, other immunoassay kit formats such as lateral flow immunochromatography have been commercialized as dipstick or cassette rapid tests. Examples are Neogen's Reveal dipstick or the Histasure cassette by Labor Diagnostika Nord (LDN). These kits promise even greater simplification of assay procedures compared to ELISA (Hungerford and Wu, 2012) however they are sensitive to temperature and humidity (Hungerford et al., 2018) which can limit their application outside of the strict ambient control of a laboratory environment. Although antibody-based kits remain popular, in recent years many commercial kits have emerged based on enzymatic detection of histamine. These new kits all use a selective and recombinant histamine dehydrogenase first described by Bakke et al. (2005). This work was refined into a well characterized method by Sato et al (2005) and first commercialized as a microplate kit by BiooScientific. Following BiooScientific's lead, commercial kit implementations use Bakke's enzyme in combination with a tetrazolium salt pro-dye that

is reduced to a colored formazan dye coupled to histamine oxidation. In contrast to antibody-based kits, the enzymatic kits give a linear response and the enzyme is used to drive conversion of histamine to completion. Most recently Bioassay Systems introduced two histamine dehydrogenase-based kits for histamine detection, one in microplate format and another as a visual endpoint test strip (Bioassay Systems, 2020). These two products have not been studied in the literature nor validated. Several test kit vendors offering enzymatic histamine assays have recently taken the additional step of validating these kits through the *Performance Tested Method* (PTM) program overseen by the AOAC Research Institute. These PTM validations include the Biofish-300 HIS, an amperometric assay by Biolan Microbiosensors (Sallares et al., 2016) and tetrazolium-based kits such as BiooScientific's MaxSignal microplate kit (Gone et al., 2017) Kikkoman's assay using a portable spectrophotometer (Shimoji et al., 2019) the RIDASCREEN® Histamine assay by R-Biopharm (Lacorn et al., 2019) and an automated procedure using the Biosystems Y15 rapid access analyzer (Dueñas et al., 2020). All of these PTM validations include data provided by an independent laboratory and confirmation data using a recognized reference method. Introduced in recent years, the BiooScientific HistaStrip dipstick assay combines the enzymatic (histamine dehydrogenase) technology described above with immobilization of the enzyme on a cotton pad attached to a test strip. This allows simplification of the procedure and the ability to detect the colorimetric response using a colorimetric strip reader. This approach differs from lateral flow immunochromatography (LFIC) test strips in several ways, including a linear response versus the sigmoidal curves generated by LFIC, much less susceptibility to temperature and humidity, and elimination of test strip positioning errors

found with strip readers and LFIC (Hungerford et al., 2018). The production of simplified, rugged, and portable test kits, combined with new approaches to sampling and extraction are required before on-site screening for histamine is practical (Hungerford et al., 1997; Hungerford, 2010, Hungerford et al, 2018).

10. Conclusion

Although histamine has many essential functions in healthy individuals, intoxications result when histamine-metabolizing enzymes are compromised or overwhelmed. This can occur either due to metabolic enzyme deficiencies such as in histamine intolerance, or from ingestion of decomposed dark-muscled fish containing high concentrations of histamine, resulting in the allergy-like symptoms of scombrotxin fish poisoning (SFP). Prevention of SFP consists of maintaining a cold chain to prevent bacterial production of histamine. The term "scombrottoxins" refers to a mixture of histamine and postulated bioactives which co-occur in decomposed scombroid fish. Two international reference methods including the CODEX recognized AOAC 977 batch fluorescence method and an EU validated HPLC method have been compared. Progress has been made on rapid methods for detecting histamine including many innovative sensors and several validated test kits based on recombinant histamine dehydrogenase.

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Highlights

- Scombrototoxin fish poisoning is also known as scombroid poisoning and histamine fish poisoning
- Scombrototoxin fish poisoning is a common cause of food poisoning worldwide
- Dietary histamine in decomposed fish is formed by bacterial enzymes and is due to mishandling
- Scombrototoxins are bioactives postulated to augment the toxicity of dietary histamine
- Many new rapid screening methods for histamine detection have been developed and validated

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Hereby, I **James Hungerford** consciously assure that for the manuscript /insert title/ the following is fulfilled:

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

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