Health promoting, safe seafood of high eating quality in a consumer driven fork-to-farm concept

EU Integrated Project no 506359

Gaps in available information on biogenic amines in seafood

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A report from RTD area 3

'Seafood safety'

Project 3.4 BIOCOM

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1. Introduction

The overall objective of the BIOOCOM-project is to provide data that will reduce the intake of biogenic amines from seafoods by European consumers and reduce the incidence of histamine fish poisoning (HFP). A major objective of the BIOCOM-project is to predict the concentration of histamine and biogenic amines in seafood at the time of consumption and this information is crucial for future assessment of the risk of HFP.

HFP is a foodborne chemical intoxication caused by eating microbiologically spoiled fish. It is a mild disease with allergic-like symptoms including rash, nausea, headache and sometimes diarrhoea. It is a common form of fish poisoning, and many incidents probably go unreported because of the mildness of the disease, lack of reporting and misdiagnosis. Histamine production in seafood is related to the histidine content of the muscle tissue, the presence of bacterial decarboxylase and environmental conditions since histamine is produced by a bacterial decarboxylation of the amino acid histidine (Lehane & Olley, 2000).

The work done within the BIOCOM-project is aimed at taking part in a risk analysis which consist of three separated but integrated parts namely, risk assessment, risk management and risk communication. The BIOCOM-project focuses on the exposure assessment (a component of risk assessment), as well as on mitigating the risk of histamine formation in seafood. Evaluating the risk associated with HFP involves estimating the severity and the likelihood of occurrence. A more unambiguous knowledge about the factors involved in HFP is needed. Even though a lot of studies have tried to elucidate the pathogenesis of HFP the problem is still unsolved. After analysing the urine of poisoned subjects, Morrow et *al*. (1991) claimed definitive evidence that histamine is the toxic agent in HFP. However many hypotheses have been put forward to explain why histamine consumed in fish is more toxic than pure histamine taken orally (Taylor & Lyons, 1983), but none has proven totally satisfactory. There is not a straight forward dose-response relationship and further investigation is required. It has been speculated if other “scombroid toxins” are acting together with histamine (Taylor, 1986; Clifford et *al*., 1991; Ijomah et *al*., 1991). Investigations concerning these speculations take part in a risk characterisation and that type of work although both relevant and interesting is not part of the present BIOCOM-project since it requires a completely different kind of science than the BIOCOM-project.

2. Identified gaps

Hereby follows the identified gaps in the literature concerning biogenic amines in seafoods. The gaps are extracted from the review in section 3.

- Factors that influence the formation of toxic concentration of histamine and biogenic amines in chilled seafood stored below 7-10°C. It is known that toxic concentration of histamine and biogenic amines can be formed in correctly chilled seafood at 0-4°C. Important information related to psychrotolerant *Morganella morganii* and *Photobacterium phosphoreum* and their histamine and biogenic amine formation is lacking and this markedly reduce our ability to assess and manage consumers’ exposure to histamine and biogenic amines in seafoods. In this area the following information is particularly lacking:

    - ❖ Techniques for simple and reliable differentiation and identification of psychrotolerant and mesophilic variants of *M. morganii*

- ❖ Enumeration methods that allow occurrence and concentrations of psychrotolerant *M. morganii* in seafoods to be determined
- ❖ Rates of growth and biogenic amine formation by psychrotolerant *M. morganii*-like bacteria as a function of temperature, atmosphere, pH and NaCl
- ❖ Combinations of temperature, atmosphere, pH and NaCl that prevent growth of psychrotolerant *M. morganii* and *P. phosphoreum*
- ❖ Seafood processing or storage conditions that inactivate psychrotolerant *M. morganii* and *P. phosphoreum*
- ❖ Variability in histamine formation between isolates of psychrotolerant *M. morganii* and isolates of *P. phosphoreum* as a function of seafood product characteristics

- Knowledge about which species of bacteria that causes HFP. Isolation and identification from leftovers from outbreaks is necessary for a better understanding of how HFP can be avoided. This knowledge could lead to more targeted and directed investigations attempting to avoid and reduce the occurrence and growth of these bacteria.

- Quantitative distribution of histamine and other biogenic amines in various seafoods

- Rapid and inexpensive methods for determination of histamine together with concentrations of other biogenic amines

- Techniques that allow the formation of histamine and other biogenic amines in seafood to be predicted at different temperatures.

3. Review:

3.1 Outbreaks

Thousands of cases of HFP have been recorded worldwide and linked to intake of seafood with high concentrations of histamine (Table 1).

Table 1 World wide outbreaks collected from publications

Seafood	Histamine (mg/kg)	Country	Year	Cases	Reference
Tuna	1190	Japan, Ogawa-machi	1955	50	(Kawabata et *al*., 1956)
Tuna	2000-9700		1973		(Kim & Bjeldanes, 1979)
Tuna	2800	USA, 4 states	1973	232	(Merson et *al*., 1974)
Tuna	6260	USA, New York City	1975	4	(Gellman et *al*., 1975)
Tuna	3250-9190	USA, San Francisco,	1977	15	(Lerke et *al*., 1978; Taylor et *al*., 1979)
Mackerel	12.5	UK	1979	1	(Murray et *al*., 1982)
Pilchard/sardines	2900 *	UK	1979	1	(Murray et *al*., 1982)
Anchovies	680	UK	1980	1	(Murray et *al*., 1982)
Pilchard	17	UK	1980	1	(Murray et *al*., 1982)
Sardines	830-1000 *	UK	1980	27	(Murray et *al*., 1982)
Sardines	150-1200 *	UK	1980	6	(Murray et *al*., 1982)

Table 1 continues on the next page

Table 1 *continued*. World wide outbreaks collected from publications

Fish	Histamine (mg7kg)	Country	Year	Cases	Reference
Sardines	720	UK	1980	2	(Murray et *al*., 1982)
Tuna	10000	UK	1980	1	(Murray et *al*., 1982)
Tuna	1050	UK	1980	4	(Murray et *al*., 1982)
Tuna	2900	UK	1980	2	(Murray et *al*., 1982)
Tuna	280	UK	1980	2	(Murray et *al*., 1982)
Tuna	35	UK	1980	1	(Murray et *al*., 1982)
Sardines	3000	UK	1981	3	(Murray et *al*., 1982)
Tuna	20	UK	1981	1	(Murray et *al*., 1982)
Tuna	16	UK	1981	1	(Murray et *al*., 1982)
Tuna	260	UK	1981	1	(Murray et *al*., 1982)
Tuna	6400	UK	1981	2	(Murray et *al*., 1982)
Mackerel	5000		1981	8	(Russell & Maretic, 1986)
Dorado	1070-1950	Japan, Yokohama	1984		(Yamanaka et *al*., 1987)
Kingfish	6000	New Zealand, Rotorua	1984	2	(Mitchell, 1984)
Bluefish	2500	USA, New Hampshire	1985	5	(Etkind et *al*., 1987)
Kahawai	2000	New Zealand, Rotorua	1985	3	(Smith et *al*., 1982)
Tuna	10-350		1986	1	(Predy et *al*., 2003)
Amberjack	2570-4300	USA, Alabama, Tennessee	1986	4	(Shaw et *al*., 1986)
Mahi Mahi	200	USA, New Mexico	1987	2	(Rieder et *al*., 1988)
Mahi mahi	500-1600	USA, Illinois,	1988	8	(Murray et *al*., 1989)
Tuna	5830-7280	USA, South Carolina,	1988	9	(Murray et *al*., 1989)
Cape	250-1625	South Africa, Cape town	1990	22	(Muller et *al*., 1992)
Kahawai	800-2540	Australia, Adelaide	1990	7	(Smart, 1992)
Sailfish	1680-1800	Taiwan western	1994	12	(Hwang et *al*., 1995)
Tuna	200	Spain, Castellon	1994	15	(Pena et *al*., 1996)
Tuna	20000	Spain	1995	14	(SanchezGuerrero et *al*., 1997)
Marlin	841	Taiwan, Taipei	1996	3	(Hwang et *al*., 1997)
Tuna	1185-2719	Taiwan Northern	1996	48	(Wu et *al*., 1997)
Marlin	841	Taiwan Northern	1996	4	(Wu et *al*., 1997)
Tuna	280-7100	UK	1996	7	(Scoging et *al*., 1997)
Tuna	1000	Denmark, Charlottenlund	1997	6	(Jeppesen, 1997)
Tuna	200	UK	1997	2	(Stell, 1997)
Tuna	2500	UK	1997	7	(Stell., 1997)
Garfish	750-900	Denmark	1997	20	(Thaysen & Sloth E., 1994)
Tuna	0-212	USA, North Carolina	1998	2	(Becker et *al*., 2001)
Tuna	2-3245	USA, North Carolina	1998	11	(Becker et *al*., 2001)
Abura-sokomutsu	7300	Japan, Tokyo	1998	21	(Kan et *al*., 2000)
Tuna	50	USA, Pennsylvania	1998	4	(Maher et *al*., 2000)
Tuna	26-372	USA, North Carolina	1999	2	(Becker et *al*., 2001)
Marlin	538-562	Taiwan, Southern	1999	256	(Su et *al*., 2000)
Tuna	250-13280	UK	1999	20	(Brett, 2000)
Sardine	3000	Japan, Osaka	2002	1	(Kanki et *al*., 2004)
Yellowfin tuna	7100-9100	Denmark, Copenhagen	2003	8	(Emborg et *al*., 2005)

*) Parallel sample: Sample taken from another fish/batch than the one involved in the outbreak

During 1990-1998 47% of all cases of fishborne (excluding molluscan shellfish) diseases in USA were caused by HFP (CSPI, 2002). Nevertheless, microorganisms responsible for histamine formation in implicated products have only been identified in a few incidents. An outbreak of HFP occurred in 1955 due to sashimi of Bigeye tuna. Kawabata et *al*. (1956) obtained 78 isolates from the sashimi involved. 11 of these were able to produce histamine. All the strains belonged to the *Proteus* family and 3 strains were identified as *P. morganii* (now *Morganella morganii*). Apart from these three strains the histamine production of other bacteria were considered low.

Lerke et *al.* (1978) and Taylor et *al*. (1979) investigated an outbreak of HFP from tuna (sashimi) in 1977 with 15 persons implicated. A strain of *Klebsiella pneumoniae* (Now *Raoultella planticola*) biotype 1 was identified as the only histamine producer among the strains isolated from the microflora. The isolation procedure was performed at 37°C which must be considered as a drawback since they could have overlooked psychrotolerant bacteria present in the tuna.

Russell & Maretic (1986) found *Enterobacter aerogenes, Escherichia coli*, *Klebsiella* sp. and other bacteria from fresh mackerel causing HFP within three families (8 persons). The strains were not tested to find the histamine producer among them, which leaves the work unfinished. Gellmann et *al*. (1975) found *Proteus* (maybe *M. morganii*) bacteria in fresh tuna involved in an outbreak of HFP in New York 1975. The strains were not further investigated. Kanki et *al*. (2004) investigated the product called iwashi maruboshi (dried sardine) because an outbreak of HFP in March 2002 in Japan occurred due to consumption of this product. From a parallel sample with a low microbial count (5.4×10^4) that contained 1700 mg/kg histamine *P. phosphoreum* was isolated and shown to produce histamine at 4°C. There is no doubt that *P. phosphoreum* is a histamine producer but considering the low microbial count and the fact that the test was performed with a parallel sample it can not be excluded that other bacteria were involved in the histamine production since the microflora must have changed due to the production process. Histamine production is typically not seen in seafood with bacterial load below 10^6-10^7 cfu/g (Lehane & Olley., 2000). Recently we performed a study with tuna involved in an outbreak in Denmark 2003 which isolated and identified *P. phosphoreum* and psychrotolerant *M. morganii* (Emborg et *al.*, 2005).

In spite of all the work done with histamine producing bacteria, information and documentation of the microflora responsible for the production of histamine in cases of HFP is lacking. Knowledge about the exact type of bacteria actually involved in different kind of seafood could lead to more targeted and directed investigations attempting to avoid and reduce the occurrence and growth of these bacteria.

The presence of other biogenic amines than histamine in seafood involved in HFP is seldom investigated. Only a few studies report these concentrations (Table 2). With such inadequate and conflicting data no conclusions on synergism can be drawn and it is clear as stated before that further information is needed. Only one recent study (Emborg et *al*., 2005) where biogenic amines other than histamine are reported has isolated and identified the micro flora involved. A more precise knowledge of the profiles of biogenic amines produced by different bacterial strains could possibly help when trying to detect histamine producing bacteria in seafoods by providing a more directed search.
Histamine and other biogenic amines concentrations can vary substantially between fishes from a single catch and even between different portions of a tuna fish (Lerke et *al*., 1978;

Frank et *al*., 1981). Specifically, Lerke et *al*. (1978) reported 52±15 mg/kg of histamine in samples from the dorsal muscle of fresh Yellowfin tuna whereas samples from the belly cavity of the same fish stored under the same conditions contained 4400±2700 mg/kg of histamine.

Frank et *al.* (1981) divided Skipjack tuna into sections and found that histamine were produced in the anterior end earlier and in higher concentrations than in the other sections where the histamine concentrations were arranged in a gradually decreasing gradient toward the posterior end of the fish. Furthermore they found that the belly flaps had histamine concentrations nearly as high as the anterior section. In contrast Middelbrookes et *al*. (1988) did not observe any significant variation in the histamine concentration between different sections of Spanish mackerel. There is no clear understanding of how the free histidine is distributed in the fish. Likewise it is not known if the content of free amino acids varies markedly with the season and between fish from the same species but from different places.

3.2 Experiments with naturally contaminated Seafood

It is obvious that factors affecting the dominating species of histamine producing bacteria in the microflora of a particular spoiling fish are many and varied. The diversity can be attributed to (i) storage times and temperature, (ii) NaCl, (iii) pH, (iv) atmosphere, (v) species of the fish and (vi) handling procedures. Many scientists believe that post-harvesting contamination is the main source of histamine producing bacteria (Lehane & Olley, 2000).

Okuzumi et *al.* (1984a) looked at the occurrence of various histamine producing bacteria on/in fish purchased from fish markets in Japan. For the summer samples *M. morganii* was the most frequently occurring bacteria followed by *P. phosphoreum*. For the winter samples only *P. phosphoreum* was detected. The study includes no information on the concentration of histamine in the fish. A later study by Okuzumi et *al.* (1984b) investigated microbial populations at various storage temperatures in mackerel and correlated the findings with the histamine concentration. Thy observed that *P. phosphoreum* dominated the microflora in fish stored at 5-10°C where 437 and 384 mg/kg respectively, of histamine was found after 7 days. At 15°C *P. phosphoreum* were still dominating particularly in the beginning of the storage although *M. morganii* increased throughout. Around 3800 mg/kg histamine were found after 4 days. At 20°C *P. phosphoreum* was dominating the microflora in the beginning of the storage, but in the later stage *M. morganii* dominated. More than 4000 mg/kg histamine were found after 2 days, and the fish showed sign of putrefaction. *P. phosphoreum* is a marine bacteria and when it produces histamine in seafood it is more likely to originate the fish raw material than from post-harvest contamination.

Ryser et *al.* (1984a) isolated 60 indigenous bacteria from frozen/thawed raw tuna and identified them as *Pseudomonas* spp. 35% produced only 32 mg/kg histamine at 21°C during 2 days and it was suggested that bacteria that grow at lower temperatures were not significant toxicologically. There seems to be discrepancy between scientists whether psychrotolerant bacteria are important for the occurrence of HFP. However, toxic concentrations of histamine have been observed in naturally contaminated seafood stored at 0-4°C (Table 3). Identification of the microflora was performed in two studies. The earliest study from 1982 resolved N-group bacteria (Okuzumi et *al*., 1982) later recognised as *P. phosphoreum* (Fujii et *al*., 1997). *P. phosphoreum* were also isolated along with *M.*

morganii in the latest study (Emborg et *al*., 2005). In the others studies identification of the microflora was not included. Additional research is needed on the importance psychrotolerant histamine producing bacteria in seafood.

From Table 4 it is obvious that temperature plays a very important role in histamine production and most cases of HFP involves seafoods stored at high or fluctuating temperatures. This is in agreement with numerous studies where Enterobacteriaceae, including *Enterobacter* spp., *M. morganii*, *Proteus* spp. and *Raoultella* spp., only produced toxic concentrations of histamine above 7-10 °C (Arnold et *al*., 1980; Wei et *al*., 1990; Oka et *al*., 1993; Gingerich et *al*., 1999). There seems to be much information concerning histamine production by mesofile bacteria, but knowledge about the psychrotolerant bacteria is lacking.

In storage trials with naturally contaminated seafood, toxic concentrations of histamine have been observed frequently at storage temperatures above 7-10 °C (Table 4) (Taylor, 1986; Frank & Yoshinaga, 1987; Flick et *al*., 2001).

Table 2 Concentrations (mg/kg) of histamine and other biogenic amines in seafood involved in outbreaks of HFP.

Seafood	Histamine	Putrescine	Cadaverine	Tryptamine	Spermine	Spermidine	Tyramine	Reference
Tuna	212	1	29					(Becker et *al*., 2001)
Tuna	298-372	1						(Becker et *al*., 2001)
Marlin	539-562	4-6	38-42	2-3	2	3-4		(Su et *al*., 2000)
Marlin	841	<1	85	16	<1	<1		(Hwang et *al*., 1997)
Marlin	841	11	85	16				(Wu et *al*., 1997)
Mahi mahi	1070-1950	30-50	170-210		20-50	30-40	50-150	(Yamanaka et *al*., 1987)
Tuna	1160	15	128		12	24		(Kim & Bjeldanes., 1979)
Tuna	1185-2719		174-309	60-228				(Wu et *al*., 1997)
Sailfish	1680-1800		110-145	1850-208	200-500	125-175		(Hwang et *al*., 1995)
Bluefish	2500	300	740					(Etkind et *al*., 1987)
Tuna	2745-3245	70.2-81.7	181.4-158.8					(Becker et *al*., 2001)
Tuna	7100-9100	14-16	27-54			4-5	53-70	(Emborg et *al*., 2005)

Table 3 Histamine concentrations in naturally contaminated seafood stored at 0- 4°C.

Seafood	Temperature (°C)	Histamine (mg/kg)	Storage time (days)	Reference
Sardines	0	1100	12	(Ababouch et *al*., 1996)
Big eye tuna	4	1000	12	(Silva et *al*., 1998)
Skipjack tuna	4	4000	12	(Silva et *al*., 1998)
Mackerel	2,5	878	10-12	(Okuzumi et *al*., 1982)
Saury	2,5	1440	10-12	(Okuzumi et *al*., 1982)
Sardines	2,5	674	10-12	(Okuzumi et *al*., 1982)
Yellowfin tuna	2	1390	10	(Emborg et *al*., 2005)
Yellowfin tuna	2	5450	24	(Emborg et *al*., 2005)

Table 4 Histamine production in various seafoods stored at different temperatures

Seafood	Temperature (°C)	Storage time (days)	Histamine (mg/kg)	Reference
Spanish mackerel	4	14	1	(Edmunds & Eitenmiller, 1975)
Spanish mackerel	20	14	238	(Edmunds & Eitenmiller., 1975)
Skipjack tuna	21	2	812	(Frank et *al*., 1983)
Skipjack tuna	25	1.5	576	(Frank et *al*., 1983)
Skipjack tuna	29	1.5	1390	(Frank et *al*., 1983)
Skipjack tuna	32	1.5	2750	(Frank et *al*., 1983)
Skipjack tuna	38	1	3430	(Frank et *al*., 1983)
Tuna	0	12	20	(Veciana-Nogués et *al*., 1997)
Tuna	8	5	110	(Veciana-Nogués et *al*., 1997)
Tuna	20	1.5	924	(Veciana-Nogués et *al*., 1997)
Skipjack tuna	-1	42	20	(Frank & Yoshinaga., 1987)
Skipjack tuna	4	24	73	(Frank & Yoshinaga., 1987)
Skipjack tuna	10	12	169	(Frank & Yoshinaga., 1987)
Skipjack tuna	0	18	3	(Rossi et *al*., 2002)
Skipjack tuna	21	2	1600	(Rossi et *al*., 2002)
Sardines	0	12	1000	(Ababouch et *al*., 1996)
Sardines	25	2	1000	(Ababouch et *al*., 1996)
Big eye tuna	4	12	2000	(Silva et *al*., 1998)
Big eye tuna	10	9	5000	(Silva et *al*., 1998)
Big eye tuna	22	5	1000	(Silva et *al*., 1998)
Skipjack tuna	4	12	4000	(Silva et *al*., 1998)
Skipjack tuna	10	9	8000	(Silva et *al*., 1998)
Skipjack tuna	22	5	3500	(Silva et *al*., 1998)
Spanish mackerel	0	16	6	(Middlebrooks et *al*., 1988)
Spanish mackerel	15	5	400	(Middlebrooks et *al*., 1988)
Spanish mackerel	30	2	250	(Middlebrooks et *al*., 1988)

3.3 Experiments with inoculated broth and seafood

The enormous literature concerning histamine producing bacteria in seafood can be divided into sub-groups which hopefully can help to elucidate what we know and what we need to find out. In this section the focus will be on psychrotolerant bacteria but some thoughts concerning mesofiles will be included. From the literature it is obvious that one of the most important bacteria when it comes to histamine production is *M. morganii*.

It seems like most of the *M. morganii* used in experiments (Table 5 and 7) belong to the mesofile variants, which are also the most well known. In 1961 Kimata (1961) described an Enterobacteriacea bacteria resembling *Proteus morganii* (now *Morganella morganii*) but was named *Acromobacter histamineum* due to optimum temperature at 20-25°C and no growth at 37° whereas Enterobacteriaceae have optimum temperatures around 37°C. Furthermore they observed a huge production of histamine, which was not known previously for this species. *A. histamineum* has since been renamed *M. morganii* (Kimata et *al*., 1958) due to great resemblance. Since these studies no one has considered heat labile *M. morganii*, but is seems like an area where further work is needed to investigate the role of this specific bacteria. However a recent and most interesting study (Emborg et *al*., 2005) has isolated and identified psychrotolerant *M. morganii* from tuna involved in an outbreak of HFP. These findings should return focus on psychrotolerant histamine producing bacteria.

Several studies have investigated *M. morganii* in inoculated seafood as well as in broth. Table 5 shows a collection of studies on histamine production by *M. morganii* in inoculated seafood stored at temperatures below 10°C.

As can be seen in Table 5 just two studies with inoculated seafood (Aytac et *al*., 2000; Emborg et *al*., 2005) have previously shown histamine production in toxic concentration by *M. morganii* at temperatures below 10°C. The reason could be that most tests with *M. morganii* are performed at elevated temperatures (25-37°C) where the psychrotolerant variants of *M. morganii* grow poorly compared to other Enterobacteriaceae. In addition most studies with *M. morganii* in seafood or broth at low temperatures (0-10°C) grew *M. morganii* at 30-37°C prior to inoculation. To our knowledge there is no information on what the effect of a shift in temperature from 37 to 2°C means on the growth and histamine production would be. Clearly further investigation with different strains of *M. morganii* is needed to identify the psychrotolerant variants.

Table 6 shows histamine production in inoculated seafood by bacteria other than *M. morganii*. It again becomes obvious that elevated temperatures are needed histamine production in most of the bacteria investigated.

Table 7 and 8 demonstrate the same patterns when broth is used as those observed in inoculated seafood. Interpretation of the results from the broth experiments must be considered more problematic, since pH, NaCl concentration and other parameters may influence the histamine production significantly.

Because of the importance of temperature in the production of histamine, several attempts have been made to estimate and predict histamine formation in spoiling fish at different temperatures. For example nomographs were constructed to predict histamine formation in Skipjack tuna and Arrhenius plots were used for such estimations in bonito and mackerel. However, the methods involved too many assumptions and were inaccurate in their predictions (Lehane & Olley, 2000). More exact information on the bacteria causing problems and the effect of varying storage conditions is needed. This information could probably lead to development of mathematical models for microbiological growth and histamine production in seafood.

Table 5 Histamine production by *Morganella morganii* in inoculated seafood stored below 10°C

Seafood	Temperature (°C)	Storage time (days)	Histamine (mg/kg)	Reference
Tuna (*Thunnus thynnus*)	0	7	0	(López-Sabater et *al*., 1995)
Yellowfin tuna (*Thunnus albacares*)	2	22	5050	(Emborg et *al*., 2005)
Yellowfin tuna (*Thunnus albacares*)	2	23	7400	(Emborg et *al*., 2005)
Yellowfin tuna (*Thunnus albacares*)	2	15	0	(Wei et *al*., 1990)
Mackerel	4	2	1624	(Aytac et *al*., 2000)
Bigeye (*Thunnus obesus*)	4	14	0	(Lorca et *al*., 2001)
Albacore	4	14	45	(Kim et *al*., 2002)
Mahi-mahi	4	14	50	(Kim et *al*., 2002)
Salmon	4	14	40	(Kim et *al*., 2002)
Mackerel	4	14	80	(Kim et *al*., 2002)
Bluefish (*Pomatomus saltatrix*)	5	7	16	(Gingerich et *al*., 1999)
Bluefish (*Pomatomus saltatrix*)	5	7	16	(Lorca et *al*., 2001)
Tuna (*Thunnus thynnus*)	8	3,5	400	(López-Sabater et *al*., 1995)
Bluefish (*Pomatomus saltatrix*)	10	5	886	(Lorca et *al*., 2001)
Bigeye (*Thunnus obesus*)	10	14	5500-6500	(Oka et *al*., 1993)
Yellowfin tuna (*Thunnus albacares*)	10	5	3000-3800	(Wei et *al*., 1990)
Bluefish (*Pomatomus saltatrix*)	10	4	338	(Gingerich et *al*., 1999)

Table 6 Histamine production by bacteria other than *Morganella morganii* in inoculated seafood below 10 °C.

Seafood	Microorganism	Temp. (°C)	Storage time (days)	Histamine (mg/kg)	Reference
Tuna (*Thunnus thynnus*)	*K. oxytoca*	0	7	0	(López-Sabater et *al*., 1995)
Tuna (*Thunnus thynnus*)	*Serratia marcescens*	0	7	0	(López-Sabater et *al*., 1995)
Tuna (*Thunnus thynnus*)	*Pleisomonas shigelloides*	0	7	0	(López-Sabater et *al*., 1995)
Yellowfin tuna (*Thunnus albacares*)	*Hafnia alvei*	2	15	80	(Wei et *al*., 1990)
Yellowfin tuna (*Thunnus albacares*)	*Klebsiella oxytoca*	2	15	90	(Wei et *al*., 1990)
Pacific makerel(*Scomber japonicus*)	Weak histamine producers at 37°	4	14	500	(Kim et *al*., 2001)
Tuna (*Thunnus obesus*)	*K. pneumoniae*	4	14	0	(Oka et *al*., 1993)
Tuna (*Thunnus obesus*)	*H alvei*	4	14	0	(Oka et *al*., 1993)
Tuna(*Thunnus thynnus*)	*K. oxytoca*	8	3,5	30	(López-Sabater et *al*., 1995)
Tuna(*Thunnus thynnus*)	*Serratia marcescens*	8	3,5	25	(López-Sabater et *al*., 1995)
Tuna(*Thunnus thynnus*)	*Pleisomonas shigelloides*	8	3,5	35	(López-Sabater et *al*., 1995)
Tuna (*Thunnus obesus*)	*K. pneumoniae*	10	14	5806	(Oka et *al*., 1993)
Tuna (*Thunnus obesus*)	*Hafnia alvei*	10	14	5532	(Oka et *al*., 1993)
Yellowfin tuna (*Thunnus albacares*)	*Klebsiella oxytoca*	10	15	3400	(Wei et *al*., 1990)
Yellowfin tuna (*Thunnus albacares*)	*Hafnia alvei*	10	15	3800	(Wei et *al*., 1990)

Table 7 Histamine production by *Morganella morganii* in broth

Temperature (°C)	Storage time (days)	Histamine (mg/kg)	Reference
0	5	0	(Kim et *al*., 2000)
0	3	0	(Behling & Taylor, 1982)
1	42	0	(Arnold et *al*., 1980)
4	-	0	(Sakabe, 1973)
4	14	0	(Kanki et *al*., 2004)
7	7	1800	(Arnold et *al*., 1980)
7	3	1332	(Behling & Taylor, 1982)
10	7	4100	(Ryser et *al*., 1984a)
10	-	0	(Torres et *al*., 2002)
10	-	0	(Sakabe., 1973)
10	5	8150	(Emborg et *al*., 2005)
10	5	9800	(Emborg et *al*., 2005)

Table 8 Histamine production by bacteria other than *Morganella morganii* in broth

Microorganism	Bacteria isolated from	Temperature (°C)	Storage time (days)	Histamine (mg/kg)	Reference
Photobacterium phosphoreum	Mackerel(scomber japonicus)	0	16	511-1460	(Morii et *al*., 1988)
Klebsiella Pneumoniae	-	0	6.5	0	(Behling & Taylor, 1982)
Citrobacter freundii	-	0	6.5	0	(Behling & Taylor, 1982)
Proteus vulgaris	Skipjack tuna (*Katsuwonus pelamis*)	1	42	0	(Arnold et *al*., 1980)
Hafnia alvei	Skipjack tuna (*Katsuwonus pelamis*)	1	42	0	(Arnold et *al*., 1980)
Stenotrophomonas maltophilia	Albacore (*Thunnus alalunga*)	4	5	26	(Ben Gigirey et *al*., 1999)
P. phosphoreum	Dried sardine	4	14	3140	(Kanki et *al*., 2004)
Proteus vulgaris		5	3	2040-6350	(Bermejo et *al*., 2002)
Pseudomonas putida		5	3	1570-2260	(Bermejo et *al*., 2002)
P. vulgaris	Skipjack tuna (*Katsuwonus pelamis*)	7	14	1800	(Arnold et *al*., 1980)
H. alvei	Skipjack tuna (*Katsuwonus pelamis*)	7	42	1000	(Arnold et *al*., 1980)
K. pneumoniae	-	7	3	1333	(Behling & Taylor, 1982)
C. freundii	-	7	3	0	(Behling & Taylor, 1982)
Enterobacter aerogenes	-	10	4	3080	(Ryser et *al*., 1984b)
K. pneumoniae	-	10	4	3180	(Ryser et *al*., 1984b)

3.4 Factors other than temperature that affect the histamine production

Ababouch et *al.* (1991a) investigated the growth of histamine producing bacteria in sardines stored in ice and at ambient temperatures (24-28°C) and at different NaCl concentrations (0% and 8%). The results showed that at ambient temperatures the growth was highly affected by the presence of 8% NaCl and the generation time doubled nearly three times. No difference in generations times at different NaCl concentrations were seen when the sardines were stored in ice, on the other hand the generation time was very long and so was the lag phase.

More investigations were performed in another study by Ababouch et *al.* (1991b). They tested *M. morganii* and two strains of *Proteus* spp. at different pH (pH 5, 6 and 7), NaCl (0, 4 and 8%) and temperature (4, 25 and 35°C). It was clear that all the factors were influencing the histamine production. The highest concentrations of histamine were found at pH 5 when the temperature was 25°C and 4% NaCl was added to the broth. This was seen in relation to all three strain tested. Lowest concentrations were observed at pH 5, 4°C and 8 % NaCl. Torres et *al*. (2002) partly support this since they saw greater histamine produced at pH 5.5 than at pH 4. A review from Arnold and Brown (1978) cite some Japanese studies from the late fifties where the histidine decarboxylase in *M. morganii* is found to have optimum activity at pH 6.0 – 6.5. Chander et *al*. (1988) investigated optimal conditions for amine production by *E. coli*. Even though *E. coli* is not a prolific histamine producer, the study found pH 5, 0.5% NaCl and 22°C to be optimal.

Since tuna are implicated in many HFP outbreaks Lopez-Galvez et *al*. (1995) investigated the effect of carbon dioxide and oxygen enriched atmospheres on the microbiological changes and changes in biogenic amines in refrigerated tuna. The study showed that the histamine production was delayed when tuna was packed in 40% CO_2/60% O_2 compared to packaging with combinations of CO_2 and air. Emborg et *al*. (2005) showed in a study using inoculated tuna that the delay in histamine production was due to inhibition of psychrotolerant bacteria (*M. morganii* and *P. phosphoreum*) when a modified atmosphere with 60% CO_2/40% O_2 was used. In vacuum packed (VP) tuna stored at 2°C both bacteria grew and produced histamine in toxic concentrations within 10 days. Wei et *al.* (1990) found no beneficial effect in controlling microbial growth and histamine production by the use of VP. They concluded that low temperature was more effective than VP.

3.5 Detection of histamine producing bacteria

Several years ago Nieven et *al*. (1981) described a medium for detection of histamine producing bacteria. The method is based on a colour change (from Bromcresol green) in the medium due to a shift in the pH value that occurs when the more alkaline histamine is formed. However, the medium has a low pH-value that could inhibit growth of some strains.

Several studies have since tried to optimize the medium because of it's tendency to give to both false positive and false negative results (Yoshinaga & Frank, 1982; Baranowski, 1985; Chen et *al*., 1989; Joosten & Northolt, 1989; Bover-Cid & Holzapfel, 1999; Actis et *al*., 1999; Mah et *al*., 2001; Mavromatis & Quantick, 2002) and some have tried alternative methods based on the same principle (Taylor & Woychik, 1982; Maijala, 1993; Leisner et *al*., 1994) but none has proven totally satisfactory. The problem in most cases is that different alkaline metabolites like ammonia are produced and causes a colour change in

the medium or that acidic metabolites mask the alkaline metabolites (Baranowski., 1985; Rodríguez-Jerez et *al*., 1994; López-Sabater et *al*., 1996; Ben Gigirey et *al*., 1999; Hernández-Herrero et *al*., 1999). da Silva et *al*. (2002) used Nivens agar to detect histamine producing bacteria from cold smoked salmon and found both false positive and false negative results. They identified *Pseudomonas* spp. and *Acinetobacter* as strong histamine producers in others test but these strains did not show a positive reaction on Nivens agar. Whether it is the identification or the medium that fails is uncertain, from our experience Pseudomonas spp. is not a strong histamine producer but at the most a weak histamine producer if any production takes place at all. Actis et *al.* (1999) used a medium with pH 6,5 and cresol red. This medium did not detect *Vibrio anguillarum* and *Acinetobacter baumannii* as histamine producers. Furthermore they observed problems with false positives, which undoubtedly could lead to serious economic losses in food industry if this medium is used.

Klausen & Huss (1987) developed a method based on conductance changes in a liquid medium at 25°C. This technique unfortunately requires expensive equipment. A drawback could also be the relatively little experience with using this method. Furthermore it is not known if psychrotolerant histamine producing bacteria will grow well at 25°C.

A molecular method for detection of histamine producing bacteria has been developed. The method allows the rapid detection of Gram-negative histamine producing bacteria by PCR and simultaneous differentiation by single-strand conformation polymorphism analysis using the amplification products of the histidine decarboxylase genes (Takahashi et *al*., 2003). In addition, a more specific molecular method for detection of *M. morganii* have been developed during the last few years. Kim et *al*. (2003a) developed at polymerase chain reaction (PCR) assay with 16S rDNA primers. The unique primers for *M. morganii* made it possible to detect levels of 10^6-10^8 cfu/ml in albacore homogenate. An enrichment step at 37°C for 6 hours made it possible to detect 9 cfu/ml. The enrichment step changes the method from quantative to qualitative. The method is not suitable for psychrotolerant *M. morganii* due to the high temperature enrichment step. Furthermore there is need for at method that detects *M. morganii* in much lower levels. The method was used to determine *M. morganii*'s origin and contamination source (Kim et *al*., 2003b). The results revealed that *M. morganii* are endogenous to the fish and pointed out the importance of sanitation in the processing plant to prevent cross-contamination.

According to Taylor (1986) many early studies of bacterial histamine production were and are still not comparative making it difficult to determine whether histamine production by bacteria were significant or not. A more standardised screening method could benefit research into histamine producing bacteria. The media used must somehow resemble the products causing HFP in orders of free amino acids, pH, NaCl and atmosphere. Moreover it is important that these factors are mentioned when describing the work done.

When it is evident which bacteria cause the most problems in seafood in relation to HFP a more direct method for detection and enumeration should be developed. It is obvious that the techniques must be simple and reliable. Furthermore an improved test for screening histamine producing bacteria, ideally encompassing and distinguishing cadaverine- and putrescine producing bacteria is needed (Lehane & Olley., 2000). It seems likely that *M. morganii* and *P. phosphoreum* plays important roles in HFP (Emborg et *al.*, 2005) thus differentiation and identification of psychrotolerant and mesophilic variants of *M. morganii* is needed due to their differential growth characteristics at low temperatures. Moreover growth rate and formation of biogenic amines as a function of temperature, atmosphere, pH and NaCl must be determined for the psychrotolerant variant of *M. morganii*.

Seafood processing or storage conditions that inactivate psychrotolerant *M. morganii* and *P. phosphoreum* especially in vacuum-packed (VP) fresh tuna is of particular importance since this product caused 50% of all HFP cases in the UK in 1996 and many cases in North America (Todd, 1997; Scoging, 1998). Furthermore it has been shown that both *M. morganii* and *P. phosphoreum* are capable of producing toxic concentrations of histamine in fresh VP tuna stored at 2°C (Emborg et *al.*, 2005). The same study point out that a modified atmosphere packaging with oxygen included delayed growth and histamine formation by both bacteria, but more studies are needed.

3.6 Detection of histamine and other biogenic amines in seafood

Fish with a high concentration of histamine are said to impart a “peppery” feel to the mouth when chewed. This feeling is easily hidden or misjudged which make tasting even on a routine basis a difficult means to use in of quality assurance (Etkind et *al.*, 1987). The classical method for determination of histamine is based on the fact that histamine causes contraction of the guinea pig ileum and this has been used for histamine analysis in fish. Many diverse methods have been published for histamine in seafood as an alternative to the guinea pig ileum method. These have often used reagents such as perchloric acid, trichloric acid, hydrochloric acid or organic solvents are used for the extraction of biogenic amines (Shalaby, 1996). Some of the important analytical methods are mentioned here:

- Fluorometric methods
  The officially accepted method for the analysis of histamine in foods in the U.S. is a fluorometric procedure that involves subjecting food extracts to an anion exchange procedure to remove interfering materials, derivatizing the histamine with *o*-phthalaldehyde, and measuring the fluorescence of the resulting compounds (Staruszkiewicz et *al.*, 1977). The method is simple, reproducible and sensitive (Taylor, 1986). An alternative procedure uses sequential extractions to remove interfering substances. After dilution the seafood are made alkaline with NaOH and saturated with Na_2CO_3. Where after it is extracted with n-butanol and 0.1 N HCl. The acid phase is assayed for histamine with *o*-phthalaldehyde (Taylor, 1986). A cation exchange procedure has also been developed (Rawles & Flick, 1996).

- Chromatographic methods
  - Semi quantitative: Thin layer chromatography (TLC)
  - Quantitative: Gas-liquid chromatography (GLC), High pressure liquid chromatography (HPLC) Ion exchange Chromatography and Capillary electrophoresis.

The quantitative methods are more elaborate than the semi quantitative. The TLC method has the advantage that it does not require expensive laboratory equipment. Numerous TLC methods have been developed for the analysis of histamine in seafoods. See review by Taylor (1986). Histamine is the only biogenic amines detected with TLC. GLC and HPLC offers usually the advantage that others biogenic amines present in the seafood are detected. Like TLC numerous methods have been developed for the use of HPLC in detection of histamine. Precolumn derivitization with *o*-phthalaldehyde or dansyl chloride has been used successfully. Post column derivtization with ninhydrin or *o*-phthalaldehyde has also been applied. Capillary electrophoresis has the advantages of being more simple and rapid than HPLC (Gardana et *al*., 1999; Lange et *al*., 2002). For review see Rawles & Flick (1996).

- Enzymatic methods/Biosensors
  Several enzymatic methods have been developed for the analysis of histamine. The methods utilize e.g. the enzyme, histamine-N-methyltransferase and radioactive S-adenosylmethionine. These systems have a high sensitivity and a total test time 12 min – 6 hours (Lehane & Olley., 2000). Furthermore biosensors where histamine is detected e.g. amperometrically at a low or high applied potential using amine oxidase immobilized on a electrode made of solid graphite or platinum or in a flow-injection analysis arrangement or on glass beads in a small reactor (Tombelli & Mascini, 1998; Niculescu et *al*., 2000). Some systems use spectrophotometric methods for detection.

A lot of effort has been put into developing a procedure that allows rapid, simple, reproducible and sensitive detection of various biogenic amines simultaneously. But improvements to these procedures are still needed to obtain a procedure that can be used worldwide within a minimum of time and with a minimum of laboratory equipment.

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