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UPLC-MS/MS determination of histamine levels in canned fish collected from Belgrade retail markets

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A b s t r a c t: The aim of this study was to determine the amount of histamine in canned fish samples collected from Belgrade retail stores using ultra-performance liquid chromatography tandem mass-spectrometry. In addition, the established levels were compared with the maximum levels set by US Food and Drug Administration (FDA) and European Union (EU) in order to assess the risk of this toxic biogenic amine to the city population. Histamine was detected in 54.07% of analyzed canned fish, in concentrations ranging from 5 to 420 mg/kg with a mean level of 60.91 mg/kg. In canned tuna, histamine levels ranged from 6 to 420 mg/kg, while in canned mackerel the concentrations ranged from 5 to 121 mg/kg. Also, the mean histamine level in canned tuna was higher than in canned mackerel (mean values were 60.91 mg/kg and 42.94 mg/kg, respectively). Among the tested canned fish, 20% of samples had higher histamine levels than the maximum level prescribed by the FDA (histamine levels >50 mg/kg), indicating definite decomposition of the fish. Histamine levels lower than 10 mg/kg were found in 51.48% of canned fish, which indicated good-quality fish products. Only 6.67% of examined production lots of canned fish had histamine levels above the regulatory limit according to the EU standard.

***Keywords:** histamine, canned tuna, canned mackerel, UPLC-MS/MS.*

Introduction

Fish and fishery products are essential for a complete diet, since they contain high amounts of proteins and free amino acids, low amounts of saturated fat and are also rich in omega fatty acids known to provide significant health benefits (*Babic et al.,* 2015; *Belicovska et al.,* 2015). On the other hand, if decomposition processes occur due to bacterial activity, enzymatic breakdown of proteins takes place, resulting in formation of biogenic amines. The enzyme histidine decarboxylase is formed during bacterial growth, and converts histidine to histamine, especially in scombroid and other fish with relatively high free histidine levels (*Zhai et al.,* 2012*)*.

Scombroid fish poisoning occurs after consumption of fish or fishery products containing relatively high histamine levels (*Lehane and Olley,* 2000). This poses a significant public health and safety concern, due to the toxicological and physiological effects, as well as being a trade issue, due to potential economic losses (*Lehane and Olley,* 2000*; Sagratini et al.,* 2012). Tuna and mackerel are the most common fish species responsible for scombroid fish poisoning (*McLauchlin et al.,* 2006). Clinical symptoms of the illness are usually mild and vary considerably, with some of the prominent ones being rash, urticaria, nausea, vomiting, diarrhea, flushing, tingling and skin itching (*Taylor, 1986*). Although all biogenic amine intakes can result in clinical symptoms due to their vasoactive effects, histamine is the most commonly found amine and the only one with regulated quantities in certain types of seafood. In relation to this, monitoring of histamine levels has also been globally accepted as one of the key parameters used to determine the safety of fish and fishery products (*Sagratini et al.,* 2012). The European Union (EU) has established an acceptable level of 200 mg/kg of histamine for fish species belonging to *Scombridae*, *Clupeidae*, *Engraulidae*, *Coryfenidae*, *Pomatomidae* and *Scombresocidae* families *(Commission Regulation (EC) No. 1441/2007)*. On the other hand, the US Food and Drug Administration (FDA) issued guidelines for fish and fishery products establishing a maximum permissible level for histamine of 50 mg/kg in any sample (*FDA,* 1995). In addition, histamine can be a very useful indicator of good manufacturing practice of canned tuna and canned mackerel fish in oil (*Frattini and Lionetti,* 1998).

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The aim of this study was to determine the amount of histamine in canned fish samples collected from Belgrade (capital of Serbia) retail stores using ultra-performance liquid chromatography tandem mass-spectrometry (UPLC-MS/MS). In addition, the established levels were compared with the maximum levels set by the FDA and EU in order to assess the risk of this toxic biogenic amine to the city population.

Materials and Methods

Sample collection

A total of 270 imported canned fish, 135 canned tuna and 135 canned mackerel, were collected from major Belgrade retail stores from 1st of July 2015 to 10th of July 2015. Samples were collected from three areas of the city. Thirty different production lots were analyzed, fifteen of each product type. The samples were collected before their expiration date, all cans were free from any physical damage and were stored at room temperature in their original packaging until analysis. After opening each can, oil was drained off, a piece of the fish muscle was taken and additionally pressed in order to remove excess oil. The analytical method used in this study was a modified method described by *Sagratini et al.* (2012). The method was validated according to the Commission Decision 2002/657/EC. All tests were performed in the Department for Residues of the Institute of Meat Hygiene and Technology, Belgrade.

Preparation of standards

Histamine stock solution was prepared by dissolving 100 mg of the analytical standard (Histamine, Sigma-Aldrich, St Louis, MO, USA) in 5% trichloroacetic acid (TCA), in 10 mL volumetric flask. The final concentration was 10 mg/mL. Stock solution was stored in the refrigerator at 4°C. The stock solution was stable for six months.

Sample extraction

A total of 1 g of each fish sample was weighed on a technical balance (Ohouse, model "Adventurer", New Jersey, USA), with an accuracy of 0.01 g in a 50 mL polypropylene tube. After addition of 10 mL 5% TCA (Sigma-Aldrich, St. Louis, MO, USA), samples were homogenized for one minute using an Ultra-Turrax S 18N-10 G (IKA-WerkeGmbh & Co., Germany) at 6000 rpm, and centrifuged at 4000 rpm for five minutes in a centrifuge (Thermo Scientific Heraeus™ model "Labofuge 200", Waltham, MA, USA). After centrifugation, supernatant was filtered through nylon syringe filters (pore diameter 0.45 mm) directly into the autosampler vials. Filtered supernatant (10 mL) was injected into the UPLC-MS/MS system.

UPLC-MS/MS

Analyses were performed on a UPLC–MS/MS instrument consisting of a Waters Acquity UPLC system (Waters, Milford, MA, USA) with quaternary pump, autosampler, column heater and triple quadrupole mass spectrometer (TQD; Waters, Milford, MA, USA). Data acquisition and analysis were performed using MassLynx® software (version 4.1, Waters). Chromatographic separation of histamine was carried-out on Purospher® Star RP-18, reversed-phase column (50 × 2.1 mm, particle size 2 mm; Merck, Darmstadt, Germany) at 35±1°C with an isocratic flow rate of 0.20 mL/min. The mobile phase consisted of 10 mM ammonium acetate and 0.1% of formic acid in water (mobile phase A) and acetonitrile (mobile phase B) in the ratio A:B = 65:35. The temperature in the autosampler was maintained at 20±1°C. Ionization of neutral molecules of histamine to molecular ions was achieved using electrospray system in a positive mode (ESI +). The temperature of the ion source was 120°C, while the temperature of the dessolvatation gas (nitrogen) was 350°C. Capillary voltage and cone voltage were 4 kV and 10 V, respectively. Argon was used as collision gas; collision energy was set to 10 V. The mass spectrometer operated in MRM (multiple reaction monitoring) mode, monitoring the m/z of the molecular ion (112 Da) and two transitional products (95 Da and 64.5 Da). The transition product of 95 Da was used for quantification.

The reported limit of quantification (LoQ) of the method was 5 mg/kg. A five-point calibration curve (including zero) was constructed by injecting a blank sample and four fortified blanks (fish muscle found to contain less than the LoQ of histamine) containing histamine standard corresponding to the final concentrations of 50, 100, 250 and 500 mg/kg. Control samples were analyzed at the beginning and end of every batch of samples. A calibration curve of histamine is displayed in Figure 1.

Results and Discussion

Histamine was detected in 146/270 (54.07%) of examined canned fish samples (Table 1), while 45.93% (n=124) of examined canned fish samples

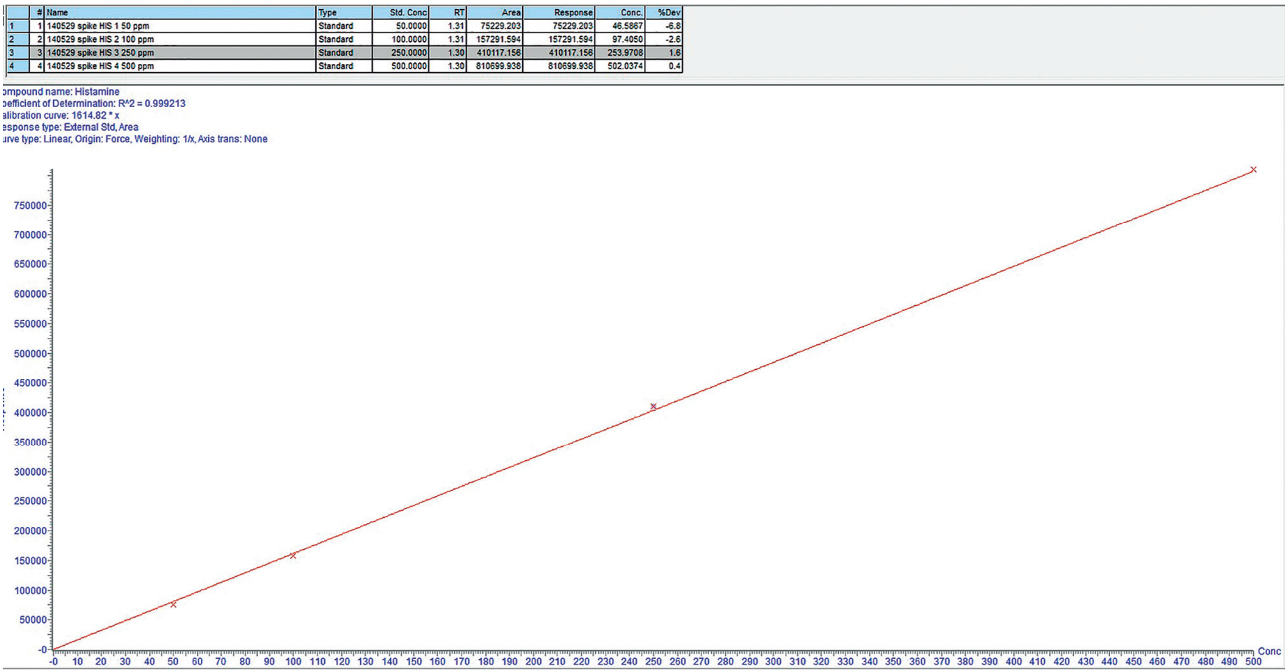

Figure 1. Calibration curve of histamine

had histamine levels below the LoQ of 5 mg/kg (Figure 2). These results differ slightly from data presented by *Karmi* (2014), who found that the overall frequency distribution rate of histamine in canned fish was 66.7%, whilst 33.3% of samples were free from histamine. However, in the study of *Kalantari et al.* (2015), histamine was detected in 78.9% of examined canned fish, which is a much higher percentage compared to the results obtained in the current study.

Statistical data for histamine concentrations in canned fish obtained from Belgrade retail markets are given in Table 1. Histamine concentrations in canned fish ranged from 5 to 420 (mean: 52.17) mg/kg. These results were higher than the results reported by *Karmi* (2014*)*, but lower than the results obtained by *Zaman et al.* (2009*)*. However, they were in agreement with the data of *Khezri et al.* (2014). Histamine levels in canned tuna, found in the present study, ranged from 6 to 420 mg/kg (Table 1). Histamine concentrations in canned mackerel ranged from 5 to 121 mg/kg (Table 1), which were higher than the results reported by *Tsai et al.* (2005). As opposed to previous studies (*Tsai et al.,* 2005*; Yesudhason et al.,* 2013; *Karmi,* 2014), the mean histamine levels in canned tuna and canned mackerel were 60.91 mg/kg and 42.94 mg/kg, respectively. In addition, canned tuna contained a higher mean histamine level than canned mackerel (60.91 mg/kg and 42.94 mg/kg, respectively), which was in line with the results of *Karmi* (2014*)*.

Five samples of canned tuna taken from Belgrade retail markets contained histamine levels higher than 200 mg/kg (ranged from 212 to 420 mg/kg). All humans are susceptible to histamine and the individual sensitivity, the amount of

Table 1. Statistical data of histamine concentrations (mg/kg) in canned fish samples obtained from Belgrade retail markets (n = 270)

	n > QL[a]	Mean for > QL[b]	SD[c]	SE[d]	Min	Max
Canned tuna (n = 135)	75	60.91	78.1	9.02	6	420
Canned mackerel (n = 135)	71	42.94	31.68	3.76	5	121
Total (n = 270)	146	52.17	60.65	5.02	5	420

[a]Number of samples with concentrations above quantification limit. [b]Mean values for samples with concentrations above quantification limit. [c]Standard deviation. [d]Standard error.

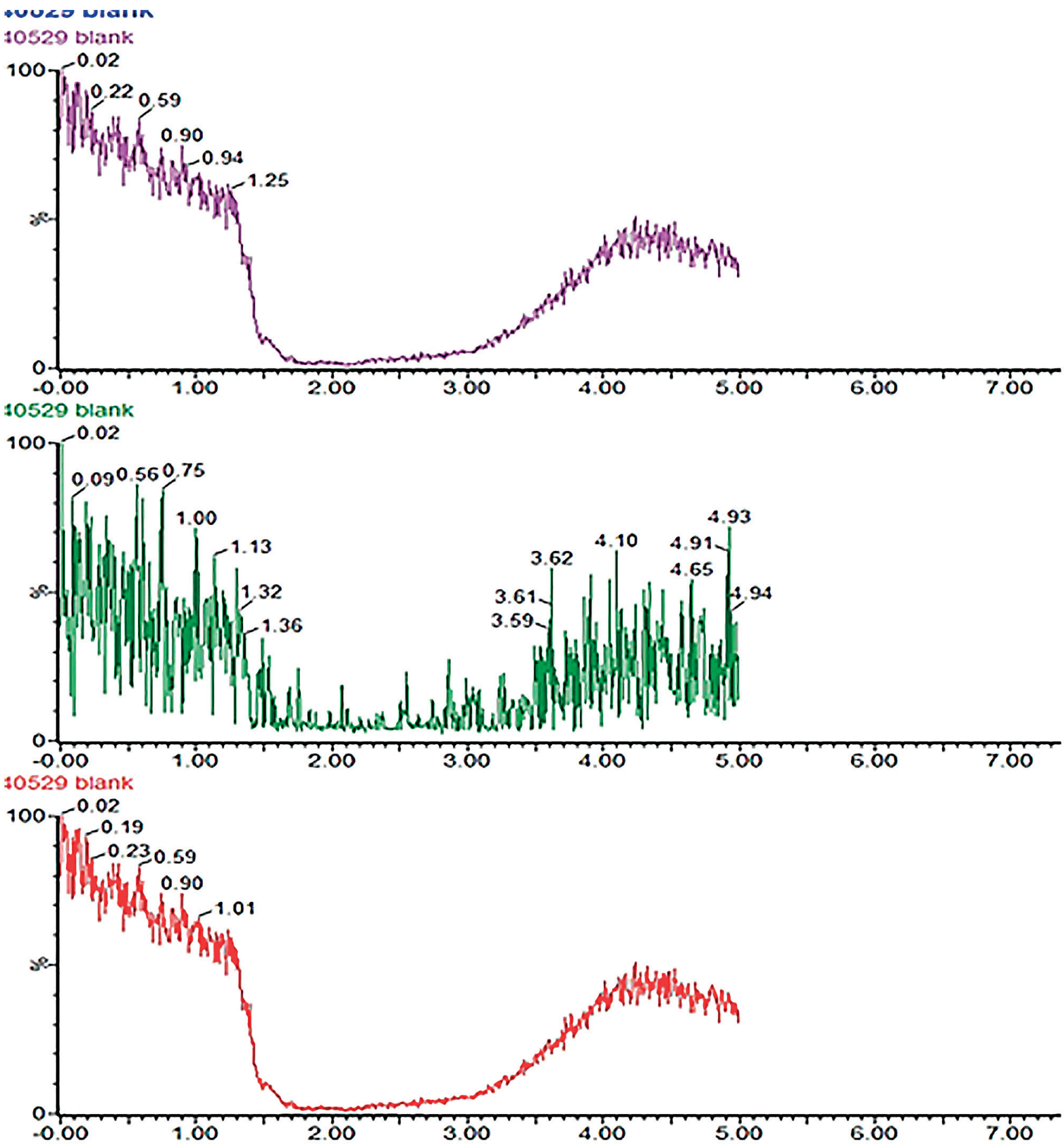

Figure 2. MRM chromatograms of histamine in canned fish sample below the LoQ

histamine in food, and the detoxification activity in the human body are the most important factors influencing the toxicological response in consumers (*Visciano et al.,* 2014). The consumption of a portion of 250 g of fish containing 200 mg/kg of histamine was reported to cause the toxicological symptoms of scombroid fish poisoning (*Centers for Disease Control and Prevention (CDC),* 2000; *Food and Agriculture Organization/World Health Organization (FAO/WHO),* 2012). Hence, this indicates that the canned fish with high histamine levels (>200 mg/kg) found in this study posed a health risk to consumers. In contrast, no sample of canned mackerel contained histamine concentrations higher than 200 mg/kg. In January 2014, an outbreak of scombroid fish poisoning occurred in 28 children (aged 2 to 5 years) who consumed canned sardines in a kindergarten in Vojvodina province, northern Serbia (*Petrovic et al.,* 2016). The authors reported that seven of the nine investigated units had histamine levels above 300 mg/kg, a concentration that leads to classical intoxication symptoms. CDC reported that scombroid fish poisoning contributes 5% of all food-related illness and 37% of all seafood-related illnesses, and cases of histamine poisoning are reported every year (*Yesudhason et al.,* 2013). Scombroid fish poisoning occurs worldwide, while the US, Great Britain and Japan are countries with the highest number of reported incidents (*Lehane and Olley,* 2000). One of the largest reported outbreaks of scombroid fish poisoning in the US occurred in August 2003 in California, where the fish samples contained markedly elevated histamine levels (from 2000 to 3800 mg/kg) (*Feldman et al.,* 2005). The European Food Safety Authority (EFSA) (*EFSA*, 2011) reported that histamine in fish or fishery products were the causative agents of more than 100 outbreaks in Europe between 2005 and 2010.

As one of the most important biogenic amines, histamine was identified by the US FDA as the major chemical hazard of seafood products (*Tao et al.,* 2011). Based on the guidelines issued by the FDA *(FDA*, 2010*)*, good-quality fishery products should contain less than 10 mg/kg of histamine, a level of 30 mg/kg indicates significant deterioration, whereas a level of 50 mg/kg is evidence of definite decomposition, and therefore, fish with this level or greater should be declared unfit for human consumption. Thus, analysis of histamine in fish and fishery products is of interest because of the toxicological risk, but also because histamine levels can be used as chemical indicators of fish spoilage, food quality and degree of freshness of the product (*Muscarella et al.,* 2013).

According to the FDA (*FDA*, 2011)*,* the number of scombrotoxin-forming fish samples necessary to make a judgment about a lot, should not be fewer than 18 samples per lot, unless the lot contains less than 18 fish, in which case a sample should be collected from each fish. In this study, there were fewer than 18 samples per lot, and therefore, each can of fish was calculated as a separate sample. The results of histamine determination in canned fish obtained from Belgrade retail markets according to the FDA criteria are depicted in Table 2. In the present study, histamine levels of less than 10 mg/kg were detected in 50.37% and 52.59% (in total, 51.48%) of examined canned tuna and canned mackerel, respectively, indicating good quality of products. The results of this study are comparable with the report by *Muscarella et al.* (2013), who found that 70% of 216 examined fish samples were good-quality fish products (histamine level<10 mg/kg). Also, in the current study, 30.37% of canned tuna and 26.67% of canned mackerel contained histamine levels between 10 and 50 mg/kg, indicating a lower quality of these products (Table 2).

As can be seen in Table 2, among the tested canned fish, a total of 54 (20.00%) exceeded the FDA regulatory limits for histamine and were unsafe for human consumption. Results from earlier studies (*Karmi et al.,* 2014; *Khezri et al.,* 2014) showed that the use of poor quality fish as raw material for canning and/or defective handling techniques of fish during processing are the main reasons of high percentage of unacceptable canned fish. Histamine levels in 26 of 135 canned tuna (19.26%) ranged from 52 to 420 mg/kg, higher than the tolerance limit of 50 mg/kg accepted by the FDA (Table 2) (Figure 3). In 28 of 135 canned mackerel fish (20.74%), histamine levels were between 50 to 121 mg/kg, which were higher than the tolerance limit of 50 mg/kg accepted by the FDA. This result is consistent with the findings reported by *Muscarella et al.* (2013), who found that 18% of fish samples were unfit for human consumption (histamine levels >50 mg/kg). Comparable results were reported by *Zarei et al.* (2011*)*, who found that 25% of tested samples had histamine levels higher than maximum levels prescribed by the FDA (*FDA*, 1995). In contrast, Yesudhason et al. (2013), *Khezri et al.* (2014) and *Kalantari et al.*

Table 2. The results of histamine determination in canned fish samples obtained from Belgrade retail markets according to the US Food and Drug Administration (n = 270)

	Histamine Levels (mg/kg)		
	n (%) < 10 [a]	**10 < n (%) < 50 [b]**	**n (%) > 50 [c]**
Canned tuna (n = 135)	68 (50.37)	41 (30.37)	26 (19.26)
Canned mackerel (n = 135)	71 (52.59)	36 (26.67)	28 (20.74)
Total (n = 270)	139 (51.48)	77 (28.52)	54 (20.00)

[a]**Good-quality fish products** – less than 10 mg/kg of histamine. [b]**Significant deterioration of fish products** – a level of histamine higher than 10 mg/kg but lower than 50 mg/kg. [c]**Unfit for human consumption** – a level of histamine higher than 50 mg/kg.

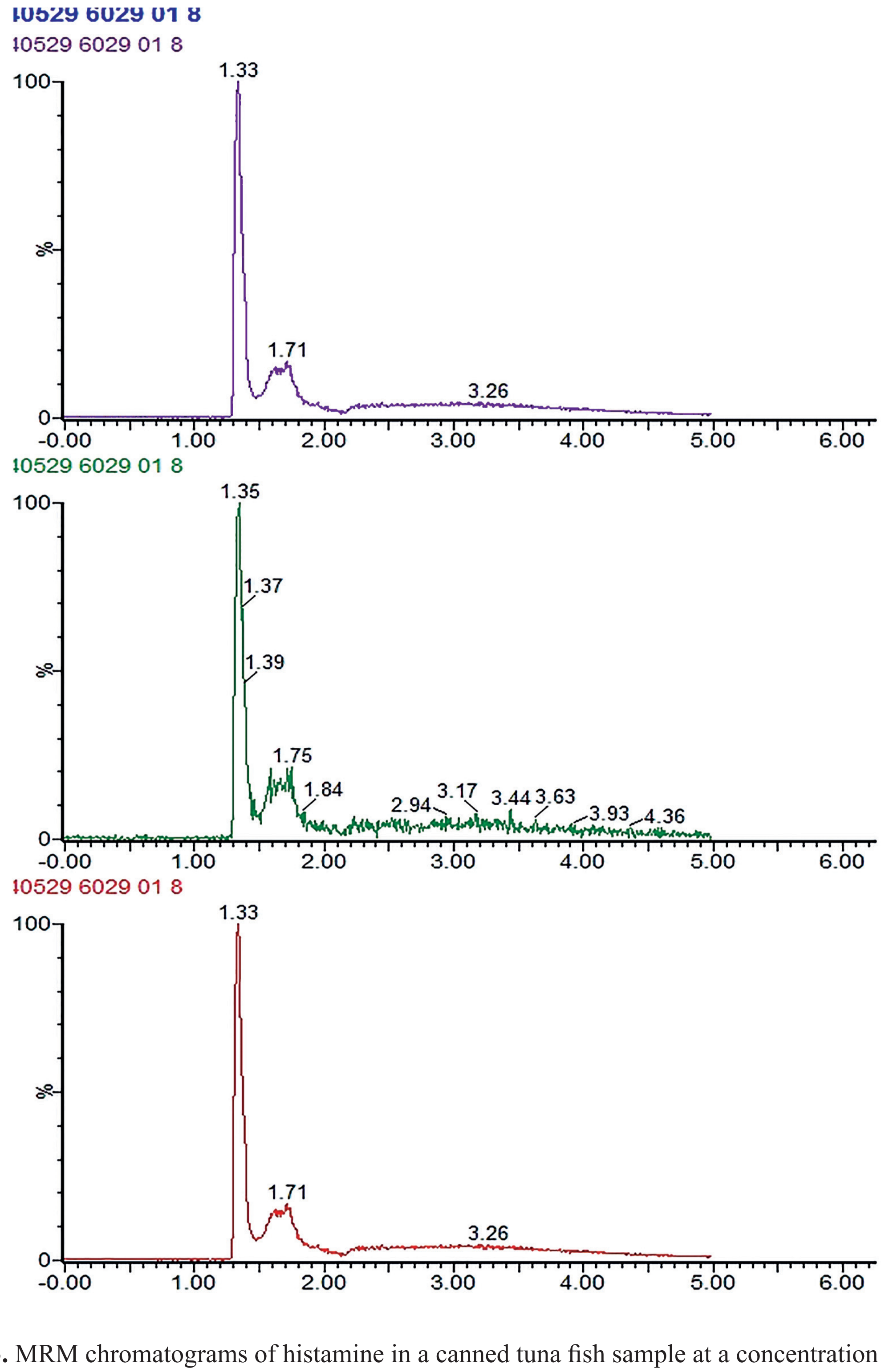

Figure 3. MRM chromatograms of histamine in a canned tuna fish sample at a concentration of 90 mg/kg. Chromatograms depict transitional products 112>95 Da, 112>64.5 Da and total ion count (TIC) of the molecular ion of histamine

(2015) found that only 0.79, 6.67% % and 3.70% of samples, respectively, exceeded the FDA regulatory limits for histamine.

The legislation in Serbia (*Official Gazette RS 72/2010*) in respect to histamine level is harmonized with the *EC Regulation 1441/2007*. The examination of one production lot includes testing of nine samples. The permitted level implies that not more than two out of nine samples can have histamine levels of more than 100 mg/kg but less than

200 mg/kg; however, no sample can have a histamine level of ≥ 200 mg/kg, and, finally, the mean histamine level of all nine samples must not exceed 100 mg/kg. Furthermore, the analysis can be performed using HPLC analytical method, or other methods. The results of histamine determination in the 30 lots of canned fish obtained from Belgrade retail markets, analyzed according to the European Commission regulation (*Commission Regulation (EC) No. 1441/2007*) are shown in Table 3. Out of 15 analyzed production lots of canned tuna, only one (6.67%) was above the regulatory limit (Table

Table 3. The results of histamine determination in canned tuna and canned mackerel of 30 lots obtained from Belgrade retail markets according to the EU standards

Lot No.	No. of units between 100 and 200 mg/kg of histamine	No. of units ≥ 200 mg/kg of histamine/	Mean value of Histamine in 9 units (mg/kg)	Lots exceeding EU tolerance limit (YES/NO)
Canned tuna				
1.	0/9	0/9	4.5	
2.	0/9	0/9	19.61	NO
3.	0/9	0/9	28.33	NO
4.	0/9	0/9	**nd**	NO
5.	0/9	0/9	**nd**	NO
6.	1/9	0/9	72	NO
7.	0/9	0/9	9.5	NO
8.	2/9	0/9	71	NO
9.	4/9	5/9	242.1	**YES**
10.	0/9	0/9	5	NO
11.	0/9	0/9	13.44	NO
12.	0/9	0/9	33.94	NO
13.	0/9	0/9	**nd**	NO
14.	0/9	0/9	12.28	NO
15.	0/9	0/9	5	NO
Canned mackerel				
1.	0/9	0/9	8.44	NO
2.	0/9	0/9	20.56	NO
3.	0/9	0/9	**nd**	NO
4.	0/9	0/9	**nd**	NO
5.	0/9	0/9	5.61	NO
6.	0/9	0/9	9.5	NO
7.	0/9	0/9	**nd**	NO
8.	0/9	0/9	47	NO
9.	0/9	0/9	4.89	NO
10.	0/9	0/9	64.67	NO
11.	0/9	0/9	69.22	NO
12.	0/9	0/9	**nd**	NO
13.	3/9	0/9	96.11	**YES**
14.	0/9	0/9	**nd**	NO
15.	0/9	0/9	18.06	NO

nd – not detected (<LoQ).

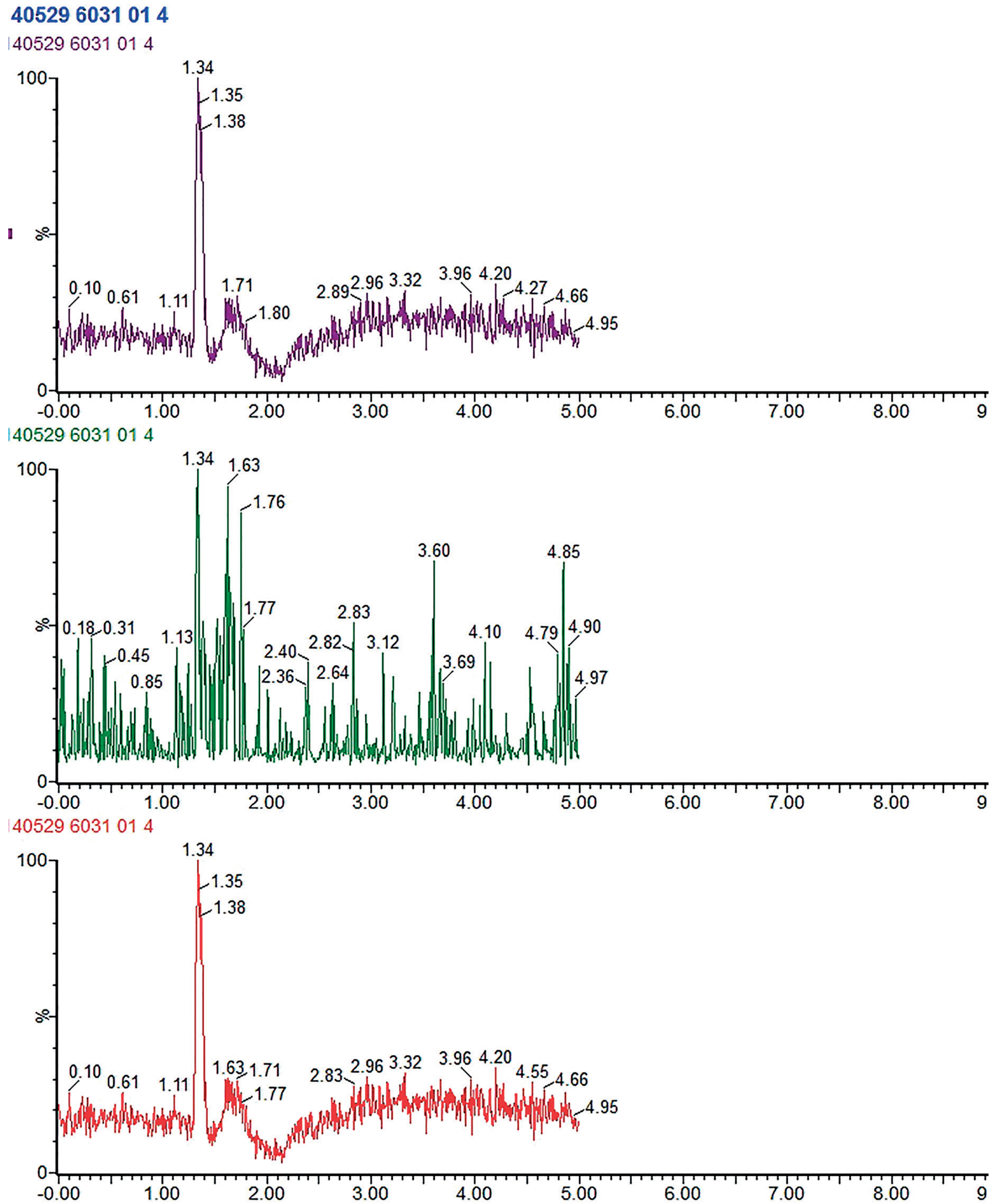

Figure 4. MRM chromatograms of histamine in a canned mackerel sample at a concentration of 5 mg/kg. Chromatograms depict transitional products 112>95 Da, 112>64.5 Da and total ion count (TIC) of the molecular ion of histamine

3). In addition, 1 of 15 (6.67%) examined production lots of canned mackerel exceeded the EU regulatory limits for histamine (Table 3) (Figure 4). Similar results were reported in the study of *Babic et al.* (2015), who found that out of 97 analyzed production lots, 3.09% were above the EU regulatory limits for histamine. Likewise, comparable results were reported by *Muscarella et al.* (2013), who found that 5% of tested samples had higher histamine levels than maximum levels prescribed by the EU (*EC Regulation 1441/2007)*. In contrast, *Kalantari et al.* (2015) found that only

0.79% of the total samples exceeded the EU regulatory limits for histamine.

On the whole, 80.00% and 93.33% of the analyzed canned fish samples were in accordance with the FDA and EU regulatory limits for histamine, respectively, indicating that the sampling scheme of US Food and Drug Administration offers more confidence that non-conforming lots will be detected *(Visciano et al.,* 2014). As stated in *EU Regulation 1019/2013*, for the detection of histamine, single samples can be taken at retail level. Despite the fact that the whole lot is not to be deemed unfit for human consumption based on the result of only one sample (unless the result is above 200 mg/kg) (*EU Regulation 1019/2013*), EU regulatory limits for histamine are fourfold higher than FDA tolerance limits (200 mg/kg and 50 mg/kg, respectively). Also, it could be argued that the possibility of preventing scombroid fish poisoning will be much higher if the FDA regulatory limits for histamine are applied, rather than the EU limits. Furthermore, on the basis of the US FDA regulatory limits for histamine, fish or fishery products can be classified according to quality, which is not the case if EU legislation is applied.

Conclusion

Histamine was detected in 54.07% of analyzed canned fish, in concentrations ranging from 5 to 420 mg/kg with a mean level of 60.91 mg/kg. In canned tuna, histamine levels ranged from 6 to 420 mg/kg, while in canned mackerel, the concentrations ranged from 5 to 121 mg/kg. Also, the mean histamine level in canned tuna was higher than in canned mackerel (mean values were 60.91 mg/kg and 42.94 mg/kg, respectively). After the histamine levels in canned fish were determined, they were compared with the FDA and EU standards. The results showed that among the tested canned fish, 20% of samples had higher histamine levels than maximum levels prescribed by the FDA (*FDA*, 1995) (histamine levels >50 mg/kg), indicating evidence of definite decomposition of product. Histamine concentrations lower than 10 mg/kg were found in 51.48% of canned fish samples, which indicated good-quality fish products. In addition, only 6.67% of examined production lots of canned fish had histamine levels above the regulatory limit according to EC Regulation 1441/2007 (*Commission Regulation (EC) No. 1441/2007*).

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