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# Sec. 540.525 Scombrotoxin (Histamine)-forming Fish and Fishery Products – Decomposition and Histamine (CPG 7108.24) Compliance Policy Guide: Guidance for FDA Staff

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*Office of Microbiological Food Safety, Office of Dairy and Seafood Safety, Division of Seafood Safety*
*Human Foods Program*
*Food and Drug Administration*
*5001 Campus Drive*
*College Park, MD 20740*
*(Tel) 240-402-2300*
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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Office of Inspections and Investigations**
**and**
**Human Foods Program**

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# Table of Contents

# Sec. 540.525 Scombrotoxin (Histamine)-forming Fish and Fishery Products – Decomposition and Histamine (CPG 7108.24) Compliance Policy Guide: Guidance for FDA Staff[1]

This compliance policy guide represents the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guide at the phone number listed on the title page.

## I. Introduction

The purpose of this compliance policy guide (CPG) is to provide guidance for FDA staff on adulteration associated with decomposition and/or histamine identified during surveillance sampling and testing of fish and fishery products susceptible to histamine formation.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

## II. Background

The composition of the muscle tissue in certain fish species, such as tuna and mahi-mahi, can cause histamine, among other spoilage compounds, to form due to the activity of enzymes produced by spoilage bacteria after the fish die. Unless these particular fish are properly chilled promptly after death and maintained in a chilled state or are otherwise treated or processed to prevent further microbial activity, histamine can accumulate in the edible muscle of these fish. Once formed, histamine cannot reliably be removed by subsequent activities, such as washing, freezing, or heating.

Properly harvested and handled fish and fishery products have little to no detectable histamine.

[1] This guidance has been prepared by the Office of Microbiological Food Safety and the Office of Policy, Regulations, and Information, both in the Human Foods Program (HFP), and the Office of Inspections and Investigations (OII), at the U.S. Food and Drug Administration.

Studies have shown that fresh scombrotoxin-forming fish contains negligible levels of free histamine[2] and that freshly caught fish must be subjected to significant time and temperature abuse to initiate the accumulation of histamine.[3] For example, one study that worked with freshly harvested live fish showed that histamine did not exceed 35 parts per million (ppm) during 24 hours of incubation until the temperatures were elevated to 23.9° Celsius (C) (75° Fahrenheit (F)) or higher throughout the exposure period; it took 12 hours at 37.8°C (100°F) to reach histamine concentrations over 35 ppm.[4] In other studies, freshly caught mahi-mahi did not form histamine above 5 ppm when held at 26°C (78.8°F) for 9 hours or more, and it took more than 6 hours for histamine to begin forming when the mahi-mahi were held at 35°C (95°F).[5] Likewise, skipjack (held for 10 hours) and yellowfin tuna (held for 12 hours) never exceeded 9 ppm histamine when held at 25°C (77°F); it took these fish more than 6 hours at 31°C (87.8°F) to accumulate more than 10 ppm histamine.[6]

The presence of 35 ppm or more histamine in fish is evidence of considerable and avoidable time and temperature exposures resulting in microbial-induced decomposition (i.e., the conversion of histidine to histamine in the fish muscle by bacterial enzymes) whether or not the decomposition is detected by sensory examination.[7] Studies show that, prior to bacterial counts in fish reaching $10^6$-$10^8$ colony forming units (CFU) per gram, histamine is not formed.[8] It is only after significant time and temperature conditions favorable to this high level of microbial growth that increased histamine in the fish begins to be detected. However, once this enzymatic trigger is initiated, the accumulation of histamine is exponential.

A 2013 report from the Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO) international group of histamine and risk assessment experts (hereafter "2013 FAO/WHO report") stated that gross time and temperature abuse during handling and storage of scombrotoxin-forming fish results in high histamine levels.[9] These experts also recognized that the recommended 200 ppm maximum histamine limit to protect health was relevant to products at the retail level—i.e., at the end of the manufacturing and distribution chain—such that more stringent requirements regarding histamine levels and sampling for the presence of

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[2] Frank, HA, DH Yoshinaga, and W Nip. 1981. Histamine formation and honeycombing during decomposition of skipjack tuna, *Katsuwonus pelamis*, at elevated temperatures. Marine Fisheries Review 43(10):9-14.
[3] *Id*.
[4] *Id*.
[5] Staruszkiewicz, W.F., J.D. Barnett, P.L. Rogers, R.A. Benner, Jr., L.L. Wong, and J. Cook. 2004. Effects of on-board and dockside handling on the formation of biogenic amines in mahimahi (*Coryphaena hippurus*), skipjack tuna (*Katsuwonus pelamis*), and yellowfin tuna (*Thunnus albacares*). J. Food Prot. 67(1):134-141.
[6] *Id*.
[7] *Id*.
[8] *See, e.g.*, Kim, SH, H An, and RJ Price. 1999. Histamine formation and bacterial spoilage of albacore harvested off the U.S. Northwest Coast. J. Food Sci. 64(2):340-343; Kim, SH, KG Field, D-S Chang, C-I Wei, and H An. 2001. Identification of bacteria crucial to histamine accumulation in Pacific mackerel during storage. J. Food. Prot. 64(10):1556-1564; López-Sabater, EI, JJ Rodríguez-Jerez, M Hernádez-Herrero, AX Roig-Sagués, and MT Mora-Ventura. 1996. Sensory quality and histamine formation during controlled decomposition of tuna (*Thunnus thynnus*). J. Food Prot. 59(2):167-174; Takahashi, H, B Kimura, M Yoshikawa, and T Fujii. 2003. Cloning and sequencing of the histidine decarboxylase genes of gram-negative, histamine-producing bacteria and their application in detection and identification of these organisms in fish. Appl. Environ. Microbiol. 69(5):2568-2579.
[9] FAO/WHO. 2013. Public health risks of histamine and other biogenic amines from fish and fishery products. Meeting report. Available at: https://www.who.int/publications/i/item/9789240691919 (hereafter "2013 FAO/WHO report").

histamine should be applied earlier in the distribution chain to ensure consumers are protected.[10]

Scombrotoxin fish poisoning (sometimes also referred to as scombroid poisoning or histamine poisoning) continues to represent the highest number of illnesses associated with finfish in the United States.[11] The 2013 FAO/WHO report found that histamine formation and scombrotoxin fish poisoning can be easily controlled and can be best mitigated by applying basic good hygienic practices and a Hazard Analysis Critical Control Point (HACCP) system, where feasible. The report concluded that the risk of scombrotoxin fish poisoning can be sufficiently mitigated for most products by rapid chilling of the fish and maintaining appropriate time and temperature controls. Additional information about scombrotoxin (histamine) formation in fish and the scombrotoxin hazard and its controls can be found in FDA's Fish and Fishery Products Hazards and Controls Guidance[12] and FDA's Bad Bug Book.[13]

Consistent with the available scientific evidence, FDA has concluded that lowering the histamine criteria for decomposition from 2 or more sample units at 50 ppm or greater to 1 or more sample unit at 35 ppm or greater is appropriate because histamine at that level indicates significant decomposition and mishandling of the fish.[14] Additionally, adoption of a 200-ppm histamine level based on the possibility of human illness at or above that level is consistent with the conclusion of the 2013 FAO/WHO report,[15] and aligns the United States with other nations.[16]

Elevated histamine can be prevented in fish by adherence to Current Good Manufacturing Practices (CGMPs) (21 CFR part 117, subpart B) and HACCP principles (21 CFR part 123) by each processor in the distribution chain. It is important to control the time and temperature of fish at each point in the distribution chain beginning with harvesters and the first receivers of fish from harvest vessels, along with the use of proper precautions by retailers and consumers. Testing of FDA's surveillance samples has shown that elevated histamine in such samples is indicative of improper harvesting, processing, and/or storage of the sampled lot or shipment. The failure to prevent histamine formation through appropriate CGMP and HACCP applications, as demonstrated by the presence of elevated histamine in the product, support a determination that the fish are adulterated under section 402(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

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[10] *Id*.
[11] Centers for Disease Control and Prevention. 2017. Surveillance for Foodborne Disease Outbreaks. Annual Report. Available at: https://www.cdc.gov/fdoss/pdf/2017_FoodBorneOutbreaks_508.pdf.
[12] FDA. Fish and fishery products hazards and controls guidance, Fourth Edition. June 2022. Available at: https://www.fda.gov/food/seafood-guidance-documents-regulatory-information/fish-and-fishery-products-hazards-and-controls.
[13] FDA. Bad Bug Book, Foodborne pathogenic microorganisms and natural toxins. 2012. Available at: https://www.fda.gov/food/foodborne-pathogens/bad-bug-book-second-edition.
[14] 2013 FAO/WHO report.
[15] *Id*.
[16] For example, the European Commission has had this threshold since 2005. *See* Commission Regulation No 2073/2005. In addition, the Codex Alimentarius standards also identify 200 ppm as a health-related threshold. *See e.g*., Codex STAN 36-1981, Standard for Quick Frozen Finfish, Uneviscerated and Eviscerated, Codex STAN 94-1981, Standard for Canned Sardines and Sardine-Type Products, Codex STAN 119-1981, Standard for Canned Finfish, Codex STAN 190-1995, Standard for Quick Frozen Fish Fillets; Codex STAN 236-2003, Standard for Boiled Dried Salted Anchovies, Codex STAN 244-2004, Standard for Salted Atlantic Herring and Salted Sprat.

# III. Policy

FDA may regard scombrotoxin-forming fish or fishery products to be adulterated within the meaning of section 402(a)(1) of the FD&C Act (21 U.S.C. 342(a)(1)) in that they bear or contain a poisonous or deleterious substance which may render them injurious to health, when histamine is present at or above 200 ppm, as established by testing.

FDA may regard scombrotoxin-forming fish or fishery products to be adulterated within the meaning of section 402(a)(3) of the FD&C Act (21 U.S.C. 342(a)(3)) in that they consist in whole or in part of any filthy, putrid, or decomposed substance, when histamine is present at or above 35 ppm or when evidence of decomposition is detected by sensory analysis.

FDA may regard scombrotoxin-forming fish or fishery products to be adulterated within the meaning of section 402(a)(4) of the FD&C Act (21 U.S.C. 342(a)(4)) in that they have been prepared, packed, or held under insanitary conditions whereby they may have become contaminated with filth, or whereby they may have been rendered injurious to health, when histamine is present at or above 35 ppm.

# IV. Regulatory Action Guidance

The following regulatory action guidance is applicable to FDA's surveillance sample test results for all fish and fishery products that are associated with scombrotoxin (histamine) formation except dried fish and fermented fish sauce/paste products that are intended for use only as condiments or as minor flavoring ingredients in other food products. Fish species associated with histamine formation and scombrotoxin (histamine) fish poisoning are listed in FDA's Fish and Fishery Products Hazards and Controls Guidance, Chapter 3, Table 3-2. Decomposition in non-scombrotoxin-forming fish and fishery products is addressed in CPG Sec. 540.370 Fish and Fishery Products – Decomposition.[17]

An appropriate FDA compliance branch may initiate an enforcement action involving any of the violative situations described in the preceding section, provided at least one of the three following general requirements is met:

## A. Decomposed

An article of scombrotoxin-forming fish or fishery products meets criterion 1. (sensory evidence of decomposition) or 2. (histamine levels as evidence of decomposition) below.

### 1. Sensory Evidence of Decomposition

Using a two-class, pass/fail evaluation approach, the presence of decomposition is detected in:

[17] FDA. CPG Sec. 540.370 Fish and Fishery Products – Decomposition. 2009. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-540370-fish-and-fishery-products-decomposition.

a. a minimum of two (2) subsamples from a lot when up to 30 subsamples are examined from the lot; or
b. a minimum of one (1) subsample from a lot when the lot consists of fewer than 30 units (fish or cartons of fish) and subsamples were collected and examined from all available units.

The presence of decomposition is detected in a subsample, i.e., the subsample "fails" the decomposition evaluation, when:

a. 20% or more of the edible portion, or portions/pieces within a subsample, contains definite and persistent sensory attributes indicative of decomposition; and/or

b. in the case of canned tuna, honeycombing of the tuna is observed;

as determined by qualified FDA seafood sensory analysts. (A current list of qualified FDA seafood sensory analysts may be obtained from HFP, Office of Laboratory Operations and Applied Science, Office of Regulatory Testing and Surveillance, Division of Science Program Coordination.)

#### 2. Histamine Levels as Evidence of Decomposition

A histamine level equal to or greater than 35 ppm is detected by original and check analysis in one (1) or more subsamples from a lot when up to 30 subsamples are analyzed from the lot. The analytical method(s) identified for histamine detection in Compliance Program (CP) CP 7303.842 should be used.

## B. Bears or Contains a Deleterious Substance

For an article of scombrotoxin-forming fish or fishery products, a histamine level equal to or greater than 200 ppm is detected by original and check analysis in one (1) or more subsamples from a lot when up to 30 subsamples are examined from the lot.

The analytical method(s) identified for histamine detection in CP 7303.842 should be used.

Documented evidence of a scombrotoxin fish poisoning associated with an article of fish, irrespective of histamine content, should be reported to the OII Office of Field Operations and Response and the Division of Seafood Safety in HFP's Office of Microbiological Food Safety, Office of Dairy and Seafood Safety.[18]

## C. Prepared, Packed, or Held Under Insanitary Conditions

For an article of scombrotoxin-forming fish or fishery products, a histamine level equal to or greater than 35 ppm is detected by original and check analysis in one (1) or more subsamples from a lot when up to 30 subsamples are examined from the lot.

[18] For more information about how to report seafood-related toxin and scombrotoxin fish poisoning illnesses, please refer to the following information on FDA's website: https://www.fda.gov/food/outbreaks-foodborne-illness/how-report-seafood-related-toxin-and-scombrotoxin-fish-poisoning-illnesses.

The analytical method(s) identified for histamine detection in the applicable CP (CP 7303.842) should be used.

**Other Considerations**

The criteria in this guidance do not establish an acceptable level of decomposition or histamine in food. Processors and owners of scombrotoxin-forming fish and fishery products are responsible for ensuring that the food complies with the FD&C Act. FDA may choose to take regulatory action against adulterated food within the meaning of the FD&C Act that does not meet the direct reference criteria in this guidance.

# V. Specimen Charges

## A. Domestic Action

### 1. Decomposed

The article of food was adulterated when introduced into and while in interstate commerce and is adulterated while held for sale after shipment in interstate commerce, within the meaning of section 402(a)(3) of the FD&C Act (21 U.S.C. 342(a)(3)) in that it consists in whole or in part of a decomposed substance.

### 2. Bears or Contains a Deleterious Substance

The article of food was adulterated when introduced into and while in interstate commerce and is adulterated while held for sale after shipment in interstate commerce, within the meaning of section 402(a)(1) of the FD&C Act (21 U.S.C. 342(a)(1)) in that it bears or contains a poisonous or deleterious substance, namely histamine, which may render it injurious to health.

### 3. Prepared, Packed, or Held Under Insanitary Conditions

The article of food was adulterated when introduced into and while in interstate commerce and is adulterated while held for sale after shipment in interstate commerce, within the meaning of section 402(a)(4) of the FD&C Act (21 U.S.C. 342(a)(4)) in that it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health.[19]

## B. Import Refusal

### 1. Decomposed

The article of food is subject to refusal of admission pursuant to section 801(a)(3) of the FD&C Act (21 U.S.C. 381(a)(3)) in that it appears to be adulterated within the meaning of section 402(a)(3) of

[19] Note, the insanitary conditions led to a histamine level greater than or equal to 35 ppm and may contribute to levels greater than or equal to 200 ppm if appropriate CGMPs and HACCP controls are not maintained.

the FD&C Act (21 U.S.C. 342(a)(3)) in that it consists in whole or in part of a decomposed substance.

### 2. Bears or Contains a Deleterious Substance

The article of food is subject to refusal of admission pursuant to section 801(a)(3) of the FD&C Act (21 U.S.C. 381(a)(3)) in that it appears to be adulterated within the meaning of section 402(a)(1) of the FD&C Act (21 U.S.C. 342(a)(1)) in that it bears or contains a poisonous or deleterious substance, namely histamine, which may render it injurious to health.

### 3. Prepared, Packed, or Held Under Insanitary Conditions

The article of food is subject to refusal of admission pursuant to section 801(a)(1) of the FD&C Act (21 U.S.C. 381(a)(1)) in that it appears to be adulterated within the meaning of section 402(a)(4) of the FD&C Act (21 U.S.C. 342(a)(4)) in that it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health.[20]

An import shipment offered for entry may be detained and subject to refusal if one or more like product forms of the same commodity in the entry appears to be adulterated (e.g., tuna sold as loins, saku blocks, steaks, cubes, poke, or ground; or one product form packaged in varying product sizes such as tuna steaks packaged as individual 4 oz., 6 oz., and 8 oz. steaks).

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[20] *Id*.
[21] *See* 47 FR 40487.
[22] Previous versions of this CPG listed dates of draft revisions to the document. Because draft documents are not operational, going forward, the revision history will only reflect the date on which revisions have been finalized. In addition, we note that not all previous revisions were published in the *Federal Register*. Where available, we have included a citation to the applicable *Federal Register* notice.
[23] *See* 60 FR 39754.