

agency is placing the environmental assessment submitted with the petition that is the subject of this notice on public display at the Dockets Management Branch (address above) for public review and comment. Interested persons may, on or before September 5, 1995, submit to the Dockets Management Branch (address above) written comments. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA will also place on public display any amendments to, or comments on, the petitioner's environmental assessment without further announcement in the **Federal Register**. If, based on its review, the agency finds that an environmental impact statement is not required and this petition results in a regulation, the notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the **Federal Register** in accordance with 21 CFR 25.40(c).

Dated: July 21, 1995.

**Alan M. Rulis,**

*Acting Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.*

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[Docket No. 95D-0157]

**Decomposition and Histamine—Raw, Frozen Tuna and Mahi-Mahi; Canned Tuna; and Related Species; Revised Compliance Policy Guide; Availability**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of revised Compliance Policy Guide (CPG) 7108.24, entitled "Decomposition and Histamine—Raw, Frozen Tuna and Mahi-Mahi; Canned Tuna; and Related Species." Revised CPG 7108.24 lowers the histamine level at which FDA may consider the fish subject to action under the Federal Food, Drug, and Cosmetic Act (the act) and states that the histamine defect action level (DAL) and the histamine action level (AL) now apply to raw, frozen tuna and mahi-mahi in addition to canned tuna. Furthermore, the revised CPG 7108.24 states that the AL

also applies to related species of raw, frozen, and canned fish implicated in instances of histamine poisoning, such as bluefish, amberjack, and mackerel, in addition to tuna and mahi-mahi. Additionally, for these related species, levels of histamine less than the AL may be considered as evidence of decomposition on a case-by-case basis when supported by additional scientific data. The title of the revised CPG reflects these changes.

**DATES:** Written comments by September 5, 1995.

**ADDRESSES:** Submit written requests for single copies of CPG 7108.24, "Decomposition and Histamine—Raw, Frozen Tuna and Mahi-Mahi and Canned Tuna; and Related Species," and Laboratory Information Bulletin no. 3794 to the Director, Office of Constituent Operations, Industry Activities Staff (HFS-565), Food and Drug Administration, rm. 5827, 200 C St. SW., Washington, DC 20204. Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments on CPG 7108.24, "Decomposition and Histamine—Raw, Frozen Tuna and Mahi-Mahi; Canned Tuna; and Related Species," to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of revised CPG 7108.24, "Decomposition and Histamine—Raw, Frozen Tuna and Mahi-Mahi; Canned Tuna; and Related Species," the *Official Methods of Analysis of the Association of Official Analytical Chemists 15th Ed.* (1990), section 977.13, and Laboratory Information Bulletin no. 3794, and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

**FOR FURTHER INFORMATION CONTACT:** Mary I. Snyder, Office of Seafood (HFS-416), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3160.

**SUPPLEMENTARY INFORMATION:** Histamine is a chemical compound that forms postmortem in the muscle of scombroid fish, such as tuna, and in other species, such as mahi-mahi, by the action of certain bacteria that are common in fish. Bacteria that have the ability to form histamine do so by the decarboxylation of L-histidine, an amino acid found in the fish muscle. The decarboxylation reaction is catalyzed by an enzyme,

histidine decarboxylase, produced by the bacteria. Fish species that are particularly vulnerable to the development of histamine are those with high levels of free L-histidine in their muscle tissues. Additional histidine may be released during decomposition and spoilage by proteolysis, whereby the protein structure is degraded, and amino acids are liberated (Ref. 1). The level of histamine produced in scombroid or other histidine-containing fish by these processes serves as an indicator of the decomposition that has occurred. When present at higher levels, histamine represents a health hazard. Therefore, FDA uses histamine to indicate that these fish are adulterated within the meaning of section 402(a)(1) and (a)(3) of the act (21 U.S.C. 342(a)(1) and (a)(3)).

In the fishing industry, decomposition and bacterial histamine production are controlled primarily by the use of low temperature storage (Ref. 2). Significant decomposition and histamine formation can be avoided by good fish handling practices including icing or rapid immersion of the catch in water chilled to -1 °C (30 °F), followed by uninterrupted frozen storage. Under high temperature storage conditions, histamine may form before other indicators of decomposition are evident, especially the odor and appearance of decomposed fish (Ref. 3).

Histamine also may form during low temperature storage conditions. However, in low temperature storage, the rate of histamine formation is slower, and it is usually accompanied by the typical odor of decomposition. Research sponsored by the Department of Health and Human Services has suggested that freezing may be more damaging to histamine-forming bacteria than it is to nonhistamine producing spoilage bacteria (Ref. 4).

Canned fish is frequently prepared from fish preserved by frozen storage before delivery to canneries. These fish are thawed before processing and are subjected to additional handling that may result in histamine levels in canned fish being somewhat higher than the levels observed in raw, freshly caught fish.

Histamine is generally not uniformly distributed in a decomposed fish. A level of less than 50 parts per million (ppm) in one section may accompany a level in excess of 1,000 ppm elsewhere in the same fillet (Ref. 3). The anterior section of an individual fish generally is higher in histamine content than the posterior section, because the intestine, which is located in the forward end, is apparently the major source of the

bacteria responsible for histamine formation. Postmortem disintegration of the intestine releases the microbial contents of the intestine which contaminate the anterior muscle tissue, making these sites particularly vulnerable to an accumulation of the amine (Refs. 5 and 6). The preponderance of scientific evidence demonstrates that the presence of histamine equal to or greater than 50 ppm, in a sample, is evidence that the fish is in a state of decomposition (Refs. 3, 5, and 6).

#### **Defect Action Level for Decomposition**

Results of research conducted in the 1970's by FDA in cooperation with major universities, industry research associations, individual canners, and the National Marine Fisheries Service demonstrate that histamine levels in freshly caught tuna and mahi-mahi are less than 1 ppm. Acceptable commercial fish generally contain about 5 ppm and rarely as much as 20 ppm histamine (Ref. 3). In a notice published in the **Federal Register** of September 14, 1982 (47 FR 40487), FDA stated that histamine levels in tuna that are judged to be of acceptable quality, based on organoleptic and physical analyses, are on the order of 10 to 20 ppm. FDA data from 1990 to 1992 show that the average histamine levels in acceptable commercial raw frozen fish (number of samples in parentheses) are 2 ppm for mahi-mahi (4), 4 ppm for albacore tuna (7), 2 ppm for yellowfin tuna (10), and 2 ppm for skipjack tuna (10) (Ref. 3). Other investigators also have reported that raw freshly caught scombroid fish contain very little histamine (Refs. 5 and 6).

FDA conducted workshops in 1974 and 1976 in association with the Tuna Research Foundation. Test packs of canned tuna were prepared by the industry and classified by FDA experts using organoleptic evaluation. The average levels of histamine in the packs of canned tuna (numbers of cans in parentheses) found to be acceptable by organoleptic evaluation were 22 ppm for albacore (36), 12 ppm for skipjack (112), and 11 ppm for yellowfin (82). The average histamine level for all 230 samples was 13 ppm. These tuna packs were not authentic packs but confirmed that commercially canned tuna of acceptable quality does not contain high levels of histamine. Similarly, commercially canned tuna collected from retail stores, in a survey conducted in 1981, was found to contain an average of approximately 6 ppm histamine (Ref. 3).

The provisions of the current CPG 7108.24 announced in the September

14, 1982, notice, established a DAL of 200 ppm histamine for canned albacore, skipjack, and yellowfin tuna. The agency also stated that it would consider regulatory action against any canned tuna found to contain between 100 and 200 ppm histamine when a second indicator of decomposition (e.g., spoilage odors or honeycomb formation) is present.

Since the studies on which the previous histamine DAL was based were conducted, the analytical methodology available for determination of histamine to 5 ppm levels has become standard practice. The official method for histamine detection published in 1977 (Ref. 7) was refined in 1993 (Ref. 8). The 1993 methodology has successfully undergone collaborative evaluation and testing. Refinement in the methodology for histamine determination and experience in using the methodology have made the determination of 50 ppm histamine levels a routine practice.

Given the findings of these studies (Refs. 3, 5, and 6); the research that shows that the histamine levels in freshly caught fish are less than 2 ppm; the fact that commercially canned tuna classified as acceptable by FDA averages 6 ppm histamine; and the fact that levels at or above 50 ppm are only found in samples classified as decomposed by FDA organoleptic expert examination, the presence of 50 ppm histamine is evidence that raw, frozen, or canned tuna, and raw or frozen mahi-mahi, are in a state of decomposition. See *United States v. 1,200 Cases, Pasteurized Whole Eggs*, 339 F. Supp. 131, 137 (N.D. Ga. 1972). Therefore, when 50 ppm or more histamine is found in these types of fish, the agency may recommend regulatory action against the fish under section 402(a)(3) of the act.

In the past two decades both industry and government have used organoleptic analysis of volatile odors for the detection of decomposition in raw and thermally processed fishery products. This analytical technique is acquired through extensive training and experience on samples and requires the analyst be periodically standardized in the application and performance of the analytical technique. However, organoleptic analysis is not quantifiable, and its application to stored and thermally processed commercial products, such as canned tuna, is difficult because the usual odors of decomposition found in raw product are often removed or altered during thermal processing. Unlike odors of decomposition, nonvolatile spoilage compounds such as histamine remain in the product and can be reliably

measured by chemical analysis (Ref. 3). Therefore, confirmatory organoleptic examination for decomposition in regulatory samples would not be necessary when histamine levels at or above 50 ppm are detected by chemical analysis.

Although the agency intends to use this DAL in deciding whether to recommend regulatory action, it does not consider that the fact that a fish or fishery product has a histamine level below 50 ppm establishes that the fish or fishery product is acceptable. Other spoilage mechanisms are possible that do not result in the formation of histamine. Thus a finding of histamine levels between 20 and 50 ppm should be viewed as indicating that the fish or fishery product has deteriorated and should cause a producer to further evaluate or test the product.

#### **Histamine Formation in Species Other Than Tuna and Mahi-Mahi**

The agency's use of histamine level as a reliable indicator of decomposition is based primarily on agency experience with tuna and mahi-mahi. However, other species have been implicated in a significant number of incidents of histamine poisoning. These other species also contain high levels of free L-histidine in their muscle tissue and are known to form histamine as they decompose. Therefore, on a case-by-case basis, when these other species contain levels of histamine equal to or greater than 50 ppm, the agency may determine that these fish are decomposed particularly when such a judgment is supported by other scientific data, including the presence of other amines associated with decomposition in these fish.

#### **Action Level for Health Hazard**

In addition to being an indicator of decomposition, when ingested at sufficiently high levels histamine causes scombroid poisoning. The term "scombroid fish poisoning" developed because fish of the families Scombridae and Scomberesocidae are commonly implicated in instances of histamine poisoning deriving from advanced stages of decomposition in these fish. Tuna and mackerel are most frequently involved in instances of histamine poisoning, but this fact is attributable, in part, to the large amounts of these species that are consumed worldwide (Ref. 9).

Nonscombroid fish, such as mahi-mahi (*Coryphaena hippurus*), is also involved in histamine poisoning. Bluefish (*Pomatomus saltatrix*) has been responsible for several scombroid poisoning outbreaks in the United States

and has caused at least one outbreak in Australia. Pink salmon, redbfish, yellowtail, marlin, and amberjack have also been implicated in scombroid poisoning outbreaks that have occurred in the United States. Outside the United States, pilchards, herring, anchovies, bluefish, and sardines have been involved in a number of cases. Sardines and pilchards have become a major source of histamine poisoning in Great Britain. Japan had an outbreak associated with black marlin, and anchovies have been implicated in single incidents in Japan, the United States, and Great Britain (Ref. 9).

From 1977 to 1981 there were 68 outbreaks of scombroid poisoning involving 461 illnesses (Ref. 10). In March 1980, the Centers for Disease Control and Prevention reported that mahi-mahi accounted for 40 percent of the scombroid poisoning outbreaks reported in the United States. Since 1980, FDA has placed most shipments of mahi-mahi offered for entry into the United States on automatic detention because of the frequent occurrence of histamine levels exceeding 500 ppm (Ref. 11).

Histamine is a poisonous or deleterious substance under section 402 (a)(1) of the act because, when ingested at sufficiently high levels, it is known to cause scombroid poisoning (Ref. 12). In the September 14, 1982, notice, the agency established, on an interim basis, an AL of 500 ppm histamine in canned tuna (47 FR 40487). At this level, the agency considers histamine to present a hazard to public health. The agency is not changing the 500 ppm AL at this time because the threshold toxic dose of histamine is not known. However, the action level for canned tuna of 500 ppm will also apply to other species of raw, frozen, and canned fish, such as mahi-mahi, bluefish, amberjack, and mackerel, all fish that have been implicated in histamine poisoning outbreaks. Furthermore, the presence of other amine decomposition products in fish may have a synergistic effect on histamine toxicity. This synergism may dramatically lower the threshold toxic dose (Refs. 9 and 10).

Therefore, FDA is revising its histamine policy and announcing the availability of revised CPG 7108.24 "Decomposition and Histamine—Raw, Frozen Tuna and Mahi-Mahi; Canned Tuna; and Related Species," which: (1) Includes a lower histamine DAL for decomposition, 50 ppm histamine rather than 100 ppm; (2) extends the application of the DAL of 50 ppm (5 mg per 100g) histamine for decomposition to raw and frozen tuna and mahi-mahi;

(3) eliminates the provision that findings of less than 200 ppm histamine need to be confirmed by organoleptic evaluation; (4) states that, on a case by case basis, histamine levels equal to or greater than 50 ppm, but less than 500 ppm, may be used as evidence of decomposition in other species commonly implicated in instances of histamine poisoning when supported by other scientific data; and (5) states that the AL of 500 ppm histamine now applies to other species of fish that have been implicated in histamine poisoning outbreaks.

#### Title of Revised CPG 7108.24

The title of CPG 7108.24 "Decomposition and Histamine in Canned Albacore, Skipjack, and Yellowfin Tuna" has been changed to "Decomposition and Histamine—Raw, Frozen Tuna and Mahi-Mahi; Canned Tuna; and Related Species" to more accurately describe the contents of the revised CPG.

#### References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Eitenmiller, R. R., and S. C. DeSouza, "Enzymatic Mechanisms for Amine Formation in Fish," in *Seafood Toxins*, edited by E. P. Ragelis, American Chemical Society, Washington, DC, pp. 431-442, 1984.
2. Behling, A. R., and S. L. Taylor, "Bacterial Histamine Production as a Function of Temperature and Time of Incubation," *Journal of Food Science* 47:1311-1314, and 1317, 1982.
3. Memorandum from Division of Science and Applied Technology (HFS-425) to Division of Programs and Enforcement Policy (HFS-415), CFSAN, FDA, dated August 6, 1992.
4. Baranowski, J. D., H. A. Frank, P. A. Brust, M. Chongsiriwatana, and R. J. Premaratne, "Decomposition and Histamine Content in Mahi-Mahi (*Coryphaena Hippurus*)," *Journal of Food Protection* 53:217-222, 1990.
5. Frank, H. A., D. H. Yoshinaga, and W-K. Nip, "Histamine Formation and Honeycombing During Decomposition of Skipjack Tuna, *Katsuwonus pelamis*, at Elevated Temperatures," *Marine Fisheries Review* 43:9-14, 1981.
6. Frank, H. A., and Yoshinaga, "Histamine Formation in Tuna" in *Seafood Toxins*, edited by E.P. Ragelis, American Chemical Society, Washington, DC, pp. 443-451, 1984.
7. Staruszkiewicz, W. F., "Fluorometric determination of Histamine in Tuna: Collaborative Study" in *Journal of the Association of Official Analytical Chemists* 60 (5) pp. 1131-1136, 1977.
8. Rogers, P. R., and W. F. Staruszkiewicz, "Modification of GLC Method for Putrescine and Cadaverine and the Fluorometric Method

for Histamine," Laboratory Information Bulletin no. 3794, July 1993.

9. Stratton, J. E., and S. L. Taylor, "Scombroid Poisoning," in *Microbiology of Marine Food Products*, edited by Ward, D. R., and C. Hackney, Van Nostrand Reinhold, New York, pp. 333-344, 1991.

10. Taylor, S. L., "Marine Toxins of Microbial Origin," *Food Technology* 42(3):94-98, 1988.

11. Regulatory Procedure Manual, part 9, Imports, Import Alert 16-05—"Automatic Detention of Mahi-Mahi Because of Histamine and Decomposition," August 14, 1991.

12. Taylor, S. L., J. Y. Hui, and D. E. Lyons, "Toxicology of Scombroid Poisoning," in *Seafood Toxins*, edited by E. P. Ragelis, American Chemical Society, Symposium Series, no. 262, pp. 417-430, 1984.

Interested persons may, on or before September 5, 1995, submit to the Dockets Management Branch (address above) written comments on the revised CPG 7108.24. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The revised CPG 7108.24 and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: July 26, 1995.

**Gary Dykstra,**

*Acting Associate Commissioner for Regulatory Affairs.*

[FR Doc. 95-19059 Filed 8-2-95; 8:45 am]

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[Docket No. 95N-0238]

#### Drug Export; Benoquin (Monobenzone U.S.P) Cream 20%

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing that ICN Pharmaceuticals, Inc., has filed an application requesting approval for the export of the human drug Benoquin (Monobenzone U.S.P) Cream 20% to Canada.

**ADDRESSES:** Relevant information on this application may be directed to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, and to the contact person identified below. Any future inquiries concerning the export of human drugs under the Drug Export Amendments Act of 1986 should also be directed to the contact person.

**FOR FURTHER INFORMATION CONTACT:** James E. Hamilton, Center for Drug