

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN¹—Continued

Type of information	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Follow up information to payors regarding previously communicated information about investigational drugs and devices.	260	2	520	2	1,040
Total	81,560

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

This draft guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR 314.81(b)(3)(i) (Form FDA 2253) have been approved under OMB control number 0910–0001.

III. Other Issues for Consideration

Although section 502(a) is specific to approved drugs and section III.A of this draft guidance addresses firms' communications of HCEI to payors only about approved drugs, FDA is interested in whether similar principles to those outlined in that section should apply to firms' communications of HCEI to payors about approved/cleared devices or whether different principles should be considered. FDA is specifically interested in identifying principles that, if applied to communications of HCEI about approved/cleared devices, could help ensure that such information is truthful and non-misleading and aids payors in making informed selection and/or coverage and reimbursement decisions about these products. FDA is interested in comments from interested parties on any of the topics addressed in this draft guidance and specifically requests comments from interested parties on the extent to which the principles provided in section III.A could be applicable to communications of HCEI about approved/cleared devices. To the extent that interested parties believe that different considerations should apply to medical devices or that guidance is needed on additional issues with respect to medical device firms' communications of HCEI about approved/cleared medical devices to payors, FDA is interested in input on those topics as well.

FDA is also seeking comments from interested parties regarding communications of HCEI about animal drugs. Although FDA recognizes that the audience for HCEI about animal drugs may be different from that identified in section III.A as a result of differences in how payment decisions are made for animal drugs, FDA is interested in learning the extent to

which the principles provided in section III.A could be applicable to communications of HCEI about animal drugs with appropriate audiences for such information. To the extent that commenters believe that different considerations should apply to animal drugs or that guidance is needed on additional issues with respect to animal drug firms' communications of HCEI about approved new animal drugs to appropriate audiences, FDA is interested in input on those topics as well.

IV. Electronic Access

Persons with access to the Internet may obtain the draft guidance at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm>, or <https://www.regulations.gov>.

Dated: January 6, 2017.

Jeremy Sharp,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2014–N–0595]

Advice About Eating Fish, From the Environmental Protection Agency and Food and Drug Administration; Revised Fish Advice; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: In June 2014, the Food and Drug Administration (FDA) and the U.S. Environmental Protection Agency (EPA) (the Agencies) jointly released a draft

update to a March 2004 document entitled “What You Need to Know About Mercury in Fish and Shellfish.” FDA and EPA are now announcing revised fish advice that contains advice and supplemental questions and answers for those who want to understand the advice in greater detail.

FOR FURTHER INFORMATION CONTACT:
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EPA: Lisa Larimer, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave. NW., MS 4305T, Washington, DC 20460, 202–566–1017, Larimer.Lisa@epa.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of June 11, 2014 (79 FR 33559), FDA, in coordination with EPA, announced the availability of the draft updated fish advice, entitled “Fish: What Pregnant Women and Parents Should Know” (the notice), and made the draft updated advice available for public comment. The draft fish advice was intended to update advice previously published by EPA and FDA in March 2004 (Ref. 1), to make it consistent with the 2010 Dietary Guidelines for Americans and to modify the wording and organization of the 2004 advice to enhance the likelihood that it would be followed by the target audience. The 2004 advice on fish consumption itself was preceded by earlier recommendations published by FDA in September 1994 and revised in May 1995 (http://www.fda.gov/ohrms/dockets/ac/02/briefing/3872_advisory%207.pdf), followed by separate, but simultaneously issued, FDA and EPA fish consumption advice in 2001. FDA's 2001 advice addressed commercial fish; EPA's 2001 advice addressed locally caught fish. The 2014 notice announcing the availability of the draft updated fish advice stated that the comment period would be open until 30 days after the last transcript became available from either the FDA Risk

Communication Advisory Committee (RCAC) meeting to be held on the draft advice or any other public meeting that the Agencies chose to hold on the draft advice (79 FR 33559). The notice also stated that the date for closure of public comment would be published in a future notice in the **Federal Register** (id.).

The RCAC meeting was held on November 3 and 4, 2014, and the transcript of the meeting became available on December 2, 2014. The meeting addressed the draft updated fish advice in great detail and included presentations by the Agencies on both the substance and the presentation of the draft updated fish advice, and included presentations by invited experts in risk communications. The meeting also provided members of the public with an opportunity to express their views to the RCAC and to officials of the Agencies who were in attendance. FDA and EPA concluded that the thoroughness of this public meeting, in addition to the public comments received and still to be received, removed the need for additional public meetings, and announced in the **Federal Register** that the comment period for the draft updated advice would be closed on March 26, 2015 (80 FR 9732). The transcript from the RCAC meeting is available electronically at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/UCM425352.pdf> and <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials>. A summary table of joint responses from FDA and EPA to the comments we received on the draft updated fish advice is available in the docket (Ref. 2). The comments themselves are also available in the Docket.

In August 2016, an external peer review of FDA-EPA's method for categorizing species of fish into consumption categories was conducted at the request of FDA and EPA. Information on the external peer review and FDA's and EPA's responses to the peer review are available at <http://www.fda.gov/fishadvice> (and also on FDA's Completed Peer Reviews page at <http://www.fda.gov/ScienceResearch/SpecialTopics/PeerReviewofScientificInformationandAssessments/ucm079120.htm>) (Refs. 3 and 4). Fish and shellfish (referred to collectively in this notice as "fish") provide protein, are low in saturated fat, are rich in many micronutrients, and provide certain omega-3 fatty acids (Ref. 5). However, as a result of natural processes and human activity, fish also contain mercury in the

form of methylmercury. Methylmercury can adversely affect the central nervous system, particularly the developing brain of the fetus. After a careful review and consideration of the RCAC transcript, the comments received on the draft updated fish advice (Ref. 2), and the peer review, EPA and FDA are issuing revised fish advice.

The 2004 advice was issued to help individuals in the target population limit their exposure to mercury while still obtaining the health benefits of fish consumption. The 2004 advice recommended avoiding four types of commercially available fish that have the highest average mercury concentrations: Tilefish, shark, swordfish, and king mackerel. The advice further recommended that women in the target population eat up to—but not exceed—12 ounces per week of most other types of commercially available fish. It recommended limiting consumption of one species, white (albacore) tuna, to no more than 6 ounces per week. For local fish caught by family and friends, the advice recommended following locally posted fish advisories regarding safe catch. Where no such advice exists, it recommends limiting consumption of locally caught fish to 6 ounces per week and eating no other fish that week.

While the 2004 advice encourages fish consumption as part of a healthy diet, it does not encourage consumption of a minimum amount of fish. In June 2014, FDA and EPA issued the draft updated advice to encourage women who are pregnant or breastfeeding to consume 8 to 12 ounces of a variety of fish per week to maximize the potential benefits that fish could provide. The Agencies also proposed to modify the wording and organization of the 2004 advice in order to enhance the likelihood that it will be followed by the target audience.

II. What is in the revised fish advice?

The revised fish advice is designed to encourage women who are pregnant and breastfeeding to consume 8 to 12 ounces of a variety of fish per week, and it includes further modified wording and organization to further enhance the likelihood that it will be followed by the target audience. The revised fish advice includes a chart and supplemental questions and answers. The chart provides recommendations for how often the target audience (pregnant women, women who might become pregnant, breastfeeding women, and young children) should eat more than 60 different fish, based on mercury concentrations.

FDA and EPA used sampling data from FDA and, to a limited extent, from

the U.S. National Marine Fisheries Service as the source for mercury amounts in fish (Ref. 6), with support from other sources (Refs. 7 through 12). The revised fish advice makes the following recommendations for the target audience:

- *Eat 2 to 3 servings a week of a variety of fish.* The revised fish advice translates the consumption target of 8 to 12 ounces of a variety of fish per week into 2 to 3 servings a week of a variety of fish, with a typical adult serving as 4 ounces. The chart in the revised fish advice shows which fish the target audience can eat 2 to 3 servings a week.

- *Eat 1 serving a week of some fish.* Since 2004, the advice has recommended limiting albacore ("white") tuna to 1 serving a week (or 6 ounces per week). The revised fish advice adds 18 fish with similar mercury concentrations to the list of fish to eat 1 serving a week.

- *Avoid certain fish with the highest mercury concentrations.* Since 1994, the advice has recommended limiting or avoiding shark and swordfish. In 2001, tilefish and king mackerel were added to this list of recommended fish to avoid. This revised fish advice adds marlin, orange roughy, and bigeye tuna, which have similar mercury concentrations. The revised fish advice recommends avoiding tilefish only from the Gulf of Mexico, consistent with the draft updated fish advice. Data on tilefish from the Atlantic Ocean indicate that these fish have much lower levels of mercury on average (Ref. 6).

- *Check for advisories for fish caught by family and friends and where no advisory exists, limit eating those fish to one serving a week and do not eat other fish that week.* The revised fish advice retains the recommendations included in the 2004 advice for fish caught by family and friends. There are waters where there may have been little or no monitoring and, therefore, the extent of potential mercury contamination is unknown. Fish caught for recreation or subsistence can contain higher levels of mercury than commercially available species.

III. How does the revised fish advice differ from the draft updated fish advice?

The revised fish advice presents the recommended consumption for more than 60 fish in a color-coded chart. The fish are presented in categories of "Best Choices," those which the target audience can eat 2 to 3 servings a week; "Good Choices," which the target audience can eat 1 serving a week; and "Choices to Avoid." See Ref. 13 for a description of how FDA and EPA

decided which fish went in each category. The draft updated fish advice recommended eating 8 to 12 ounces of a variety of fish per week and choosing fish lower in mercury, but it only mentioned 7 of those fish (salmon, shrimp, pollock, tuna (light canned), tilapia, catfish, and cod). The revised fish advice also retains the recommendation to eat a variety of fish. The revised fish advice adds 18 fish that the target audience can eat 1 serving a week (see “Good Choices” category in the revised fish advice). The draft updated fish advice included only white (albacore tuna) as a fish to limit to 6 ounces per week. Another change between the draft updated advice and the revised fish advice is that the revised fish advice adds marlin, orange roughy, and bigeye tuna to the list of fish that the target audience should avoid eating (see “Choices to Avoid” category in the revised fish advice). These fish were added because they have comparable mercury levels to fish included in the draft updated advice as fish that should be avoided (*i.e.*, shark, swordfish, tilefish from the Gulf of Mexico, and king mackerel).

The Agencies reorganized the questions and answers (Qs and As) into topic areas, simplified the responses, and added new questions as a result of comments received during the comment period. The chart includes a link to two fish advice Web sites (<http://www.fda.gov/fishadvice>) and <http://www.epa.gov/fishadvice>), images to show serving size, and is designed to make it clear and easy to read for display at point of sale, doctors’ offices and elsewhere. The Web site contains the advice and the Qs and As. Educational and outreach materials will be added to the Web site as they are developed.

IV. What comments were received and how does the revised fish advice reflect them?

FDA and EPA received over 200 comments from States, industry, academia, various organizations, and concerned individuals. The comments covered a range of topics from the scientific basis of the advice to communication. There was a wide range of opinions expressed in the comments, not all of which were relevant to the advice. The majority of the comments pertained to the clarity and effectiveness of how the advice was presented. In response to comments, the Agencies revised the presentation of the advice, as discussed in part III of this document. Other comments suggested a more restrictive set of consumption recommendations or disagreed with

setting consumption thresholds for specific species of fish or for any but the species highest in mercury. After reviewing the comments, FDA and EPA adopted an approach in which fish species are separated into three categories based on average measured mercury content (“Best Choices,” “Good Choices,” and “Choices to Avoid”). An evaluation of available information led the Agencies to recommend eating 2 to 3 servings a week for some fish and 1 serving a week for others. The advice to eat 2 to 3 servings of a variety of fish a week is consistent with the recommendation in the 2015–2020 Dietary Guidelines for Americans that women who are pregnant or breastfeeding consume at least 8 and up to 12 ounces of a variety of fish lower in mercury per week. Consuming 8 to 12 ounces of fish per week while pregnant or breastfeeding would be a significant dietary change for most women. In a survey of over 1,200 pregnant women conducted by FDA in 2005, median fish consumption was 1.8 ounces per week (Ref. 14).

The approach in the revised fish advice differs from that taken in the draft updated fish advice not only in that it categorizes more than 60 fish types, but also in its analytical basis. In categorizing the fish species for recommended consumption, the revised fish advice compares the reference dose (RfD) developed by EPA (Ref. 15) to the predicted exposure from the consumption of different fish species. Because the RfD is a rate of exposure that a person can experience over a lifetime without appreciable risk of harm and includes a 10-fold uncertainty factor to allow for variability among individuals and groups, this was a highly protective approach for determining which fish belong in each category. Specifically, the RfD for mercury is protective of neurodevelopmental effects from a critical window of development for a fetus during pregnancy. We believe the new approach is more protective of public health. This new approach is also consistent with a number of the comments received, and the external peer review conducted.

V. What did the peer reviewers say and how did FDA and EPA respond?

Overall, the reviewers agreed upon the necessity of mercury fish advice for pregnant women, those trying to get pregnant, and children, to encourage fish consumption while helping to avoid mercury. The reviewers were generally supportive of the technical information and methodology used to support the scientific basis for the fish

consumption recommendations. The reviewers made suggestions to improve clarity, transparency, and presentation, and to enhance the scientific underpinnings of the fish advice. The reviewers suggested supplementing FDA’s data on mercury levels in seafood with other published sources to support the fish categorization for species with small sample sizes and/or large variability in mercury levels. The reviewers also provided various suggestions of where additional details could be added to aid the reader and support the conclusions. FDA and EPA implemented many of the reviewers’ recommendations. A report of the FDA–EPA response to the peer review is available at <http://www.fda.gov/fishadvice> (and also on FDA’s Completed Peer Reviews page at <http://www.fda.gov/ScienceResearch/SpecialTopics/PeerReviewofScientificInformationandAssessments/ucm079120.htm>) (Ref. 4).

VI. How can I access the documents?

The revised fish advice and supplemental questions and answers are available electronically at <http://www.fda.gov/fishadvice> and <http://www.epa.gov/fishadvice>.

VII. References

The following references are on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852 and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the **Federal Register**, but Web sites are subject to change over time.

1. “What You Need to Know About Mercury in Fish and Shellfish; 2004 EPA and FDA Advice for: Women Who Might Become Pregnant, Women Who are Pregnant, Nursing Mothers, Young Children,” available at <http://www.fda.gov/food/foodborneillnesscontaminants/buystoresservesafefood/ucm110591.htm>.
2. Summary Table of Responses to Public Comments on EPA’s and FDA’s Draft Updated Advice About Eating Fish (Docket No. FDA–2014–N–0595).
3. External Peer Review of FDA/EPA’s “Technical Information on the Development of Fish Consumption Advice,” available at <http://www.fda.gov/fishadvice> and <http://www.fda.gov/ScienceResearch/SpecialTopics/PeerReviewofScientificInformationandAssessments/ucm079120.htm>.
4. FDA and EPA’s Response to External Peer

Review on the FDA-EPA's Technical Information on the Development of Fish Consumption Advice, available at <http://www.fda.gov/fishadvice> and <http://www.fda.gov/ScienceResearch/SpecialTopics/PeerReviewofScientificInformationandAssessments/ucm079120.htm>.

5. Institute of Medicine, Committee on Nutrient Relationships in Seafood: "Selections to Balance Benefits and Risks," (2007). Seafood Choices, Balancing Benefits and Risks. The National Academies Press, Washington, DC.
6. "Mercury Levels in Commercial Fish and Shellfish 1990–2010," available at <http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm115644.htm>.
7. Karimi, R., Fitzgerald, T.P., and Fisher, N.S. (2012). "A Quantitative Synthesis of Mercury in Commercial Seafood and Implications for Exposure in the United States." *Environ Health Perspect* 120, 1512–1519, available at <http://ehp.niehs.nih.gov/1205122/>.
8. U.S. Environmental Protection Agency (U.S. EPA) 2003. Mercury in Marine Life Database. Office of Wetlands, Oceans and Watersheds, available at https://cfpub.epa.gov/si/si_public_record_Report.cfm?dirEntryId=58213.
9. U.S. Environmental Protection Agency. (U.S. EPA) (2016). National Coastal Assessment (NCA): Northeast 2000–2006 Summary Data, available at <https://archive.epa.gov/emap/archive-emap/web/html/index-124.html>.
10. U.S. Environmental Protection Agency (U.S. EPA). (2016). National Coastal Condition Assessment (NCCA) Office of Water & Office of Research Development, EPA 841-R-15-006, Washington, DC. 2010 Results, available at <https://www.epa.gov/national-aquatic-resource-surveys/national-coastal-condition-assessment-2010-results>.
11. Health Canada, (2007) Human Health Risk Assessment of Mercury in Fish and Health Benefits of Fish Consumption, Bureau of Chemical Safety Food Directorate Health Products and Food Branch, Ottawa, Ontario, Canada.
12. Cladis, D.P., Kleiner, A.C., and Santerre, C.R. (2014). "Mercury Content in Commercially Available Finfish in the United States." *J Food Prot* 77, 1361–1366, available at <http://www.ncbi.nlm.nih.gov/pubmed/25198598>.
13. FDA-EPA Fish Advice: Technical Information, available at <http://www.fda.gov/fishadvice>.
14. Lando, A.M., S.B. Fein, and C.J. Choinière, "Awareness of Methylmercury in Fish and Fish Consumption Among Pregnant and Postpartum and Women of Childbearing Age in the United States," *Environmental Research*, vol. 116, pp. 85–92, 2012.
15. U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS), available at <http://www.epa.gov/iris/subst/0073.htm>.

Dated: January 11, 2017.

Jeremy Sharp,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2016–D–4482]

Regulation of Mosquito-Related Products; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry (GFI) #236 entitled "Regulation of Mosquito-Related Products." This draft guidance provides information regarding regulatory oversight of mosquito-related products, defined as those articles for use in or on mosquitoes. We are clarifying circumstances under which such products are regulated by FDA as new animal drugs under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and other circumstances under which such products are regulated by the Environmental Protection Agency (EPA) as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by February 21, 2017.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal:* <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any

confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA–2016–D–4482 for "Regulation of Mosquito-Related Products." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- *Confidential Submissions—*To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can