

the agency must be accompanied by the certification. On April 18, 2008, FDA published a draft guidance on the certification requirement. In the draft guidance FDA provided a list of the types of submissions and applications that typically did *not* need to be accompanied by a certification. We received a number of comments to the docket concerning whether a certification should accompany the types of submissions and applications listed in the draft guidance, as well as other types of documents and information submitted to FDA. We also received a number of comments on this issue during the process for obtaining clearance under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520) for the certification form itself. In addition, FDA also has had more experience with the submission of the certification form since the form was implemented.

The comments we received in response to the draft guidance and the development of the certification form, the inquiries to the agency, and our evolving experience caused us to reconsider our initial approach of identifying those documents and information that did not need to be accompanied by a certification. Instead, we concluded that it was more useful to identify those applications and submissions that must be accompanied by a certification. This approach is also consistent with many of the comments, which asked that we provide more specific information than was included in the draft guidance. Thus, we intend to exercise enforcement discretion concerning the submission of a certification with certain categories of applications and submissions to FDA, as noted in the guidance.

This guidance describes FDA's current thinking, for purposes of implementing Title VIII of FDAAA, regarding specific types of applications and submissions submitted to FDA under section 505, 515, 520(m), or 510(k) of the act, or under section 351 of the PHS Act, and accompanying certifications described in section 402(j)(5)(B) of the PHS Act, 42 U.S.C. 282(j)(5)(B). We note that the Agency's discussion of "applications" and "submissions" in this guidance is not necessarily applicable to any other provision of law. In determining how to interpret the certification requirement, FDA has focused on the plain language of Title VIII of FDAAA, as well as information that Title VIII is intended to capture.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115).

The guidance represents the agency's current thinking regarding the certification requirement in section 402(j)(5)(B) of the PHS Act (42 U.S.C. 282(j)(5)(B)). It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of applicable statutes and regulations.

## II. Comments

Interested persons may, at any time, submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding the guidance. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. A copy of the guidance and received comments are available for public examination in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

## III. Paperwork Reduction Act of 1995

This guidance refers to a previously approved collection of information. This collection of information is subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The collection of information has been approved under OMB Control No. 0910–0616.

## IV. Electronic Access

Persons with access to the Internet may obtain the guidance document at either <http://www.fda.gov/oc/initiatives/advance/fdaaa.html> or <http://www.regulations.gov>.

Dated: January 15, 2009.

**Jeffrey Shuren,**

*Associate Commissioner for Policy and Planning.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA–2009–N–0018]

#### **Report of Quantitative Risk and Benefit Assessment of Commercial Fish Consumption, Focusing on Fetal Neurodevelopmental Effects (Measured by Verbal Development in Children) and on Coronary Heart Disease and Stroke in the General Population, and Summary of Published Research on the Beneficial Effects of Fish Consumption and Omega-3 Fatty Acids for Certain Neurodevelopmental and Cardiovascular Endpoints; Availability**

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

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of two draft documents. The first is entitled "Report of Quantitative Risk and Benefit Assessment of Commercial Fish Consumption, Focusing on Fetal Neurodevelopmental Effects (Measured by Verbal Development in Children) and on Coronary Heart Disease and Stroke in the General Population" (draft risk and benefit assessment report). The draft risk and benefit assessment report describes an analysis done by FDA that results in quantitative estimates of the net effect on fetal neurodevelopment in children of maternal consumption of commercial fish, as measured by verbal development and the net effect of eating commercial fish on coronary heart disease and stroke in the general population. Effects with respect to each of these health endpoints has been associated in the scientific literature with methylmercury exposure (which primarily occurs through fish consumption) and with the consumption of fish and of omega-3 fatty acids, which are found in fish. The second draft document entitled "Summary of Published Research on the Beneficial Effects of Fish Consumption and Omega-3 Fatty Acids for Certain Neurodevelopmental and Cardiovascular Endpoints" (draft summary of published research) is a compendium of research prepared by FDA for use in developing its quantitative risk and benefit assessment. When peer and public review are complete, the draft risk and benefit assessment report and the draft summary of published research are intended to add to the growing body of scientific literature investigating the

likelihood, magnitude, and direction of health impacts linked to consumption of commercial fish. FDA is seeking public comment on the draft risk and benefit assessment report and the draft summary of published research.

**DATES:** Comments on the draft risk and benefit assessment and on the draft summary of published research must be submitted by April 21, 2009.

**ADDRESSES:** Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>.

**FOR FURTHER INFORMATION CONTACT:** Philip Spiller, Center for Food Safety and Applied Nutrition (HFS-002), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835, 301-436-1428, FAX 301-436-2668, e-mail: [Philip.Spiller@fda.hhs.gov](mailto:Philip.Spiller@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:**

**I. Background**

Fish provides protein, is low in saturated fat, and is rich in many micronutrients; it also can be a source of certain omega-3 fatty acids. As the Institute of Medicine of the National Academies of Science (IOM) noted in a recent report, “[i]n the past several years, research has implicated seafood, particularly its contribution of EPA and DHA [two omega-3 fatty acids], in various health benefits identified for the developing fetus and infants, and also for adults, including those at risk for cardiovascular disease.” (Institute of Medicine, Committee on Nutrient Relationships in Seafood: Selections to Balance Benefits and Risks. *Seafood Choices: Balancing Benefits and Risk*. 2006, National Academy of Sciences, at 1). However, as a result of natural processes and human activity, aquatic food sources, including fish, can contain methylmercury, which has been linked to adverse health consequences. Because of the presence of methylmercury in fish, FDA and the U.S. Environmental Protection Agency (EPA) issued an advisory to consumers, “What You Need to Know About Mercury in Fish and Shellfish” (<http://www.cfsan.fda.gov/~dms/admeHg3.html>). The advisory, which was most recently revised in 2004, recommends that women who may become pregnant, pregnant women, nursing mothers, and young children avoid some types of fish and eat fish and shellfish that are lower in methylmercury, as specified in more detail in the advisory.

Researchers in the United States and elsewhere have attempted in recent years to develop approaches to better evaluate the net health impacts of fish consumption; in other words, to understand the relationship between the risk of not eating fish (and thus losing any health benefits fish may provide) and the risk of eating fish that contains methylmercury at the levels currently found in the commercial fish available to consumers. As the IOM noted in its 2006 report, “A better way is needed to characterize the risks combined with the benefits analysis.” (IOM 2006 at 6). The draft summary of published research and the draft risk and benefit assessment report were developed by FDA to provide further scientific information to help address this question for consumers of commercial seafood in the United States (i.e., fish shipped or sold interstate, as opposed to fish caught recreationally or for subsistence).

The draft risk and benefit assessment report reflects an effort by FDA to quantify the impact of eating commercial fish on three human health endpoints: (1) Neurodevelopment, as measured by verbal development in childhood as assessed by the effect of prenatal exposure to methylmercury as passed from the mother to the developing fetus; (2) risk of fatal coronary heart disease; and (3) risk of fatal stroke. Each of these health endpoints has been associated in the scientific literature both with adverse effects of methylmercury exposure (including through fish consumption) and beneficial effects of regular fish consumption. The draft risk and benefit assessment report provides further scientific information about the likelihood and magnitude of either beneficial or adverse net effects on health at current levels of commercial fish consumption and exposure to methylmercury through fish consumption in the United States. The draft risk and benefit assessment report should not be construed as altering the existing fish advisory. Moreover, because this assessment does not distinguish among types of fish in terms of their beneficial constituents, it is not possible to translate the results of this analysis into fish-specific advice to consumers about maximizing benefits.

The methodology used for the quantitative risk and benefit assessment is novel for FDA in that, rather than attempting to quantify the risk resulting from the presence of a particular hazard in a food, it estimates that risk and the benefit from consumption of the food in the same quantitative analysis. For fetal neurodevelopment, the assessment

estimates this net effect by separately estimating: (1) The likelihood and size of an adverse contribution from methylmercury to the net effect; (2) the likelihood and size of a beneficial contribution to the net effect from fish; and (3) the likelihood, size, and direction of the net effect. For the methylmercury contribution, the assessment uses data to derive modeling estimates of the association between methylmercury and early age verbal skills (as an indicator of neurodevelopment) and then compares the results against results developed elsewhere on methylmercury’s effect on other aspects of neurodevelopment, including intelligence quotient (IQ). For the fish contribution, the assessment uses data to derive modeling estimates of the association between fish consumption during pregnancy and early age verbal skills. For the net effect, the assessment combines the results from the methylmercury and fish contributions. This draft risk and benefit assessment report builds on published work performed previously by FDA scientists on the estimation of a methylmercury effect, as well as recent articles by other investigators that have quantitatively assessed this effect. For fatal coronary heart disease and stroke, the assessment estimates the net effect on risk from fish consumption without separately modeling a methylmercury contribution and a fish contribution. Most data on this subject come from studies that measured an association between fish consumption and these health endpoints without measuring a methylmercury contribution. The modeling builds in part on dose-response functions for these endpoints that have been published in the scientific literature.

The draft risk and benefit assessment report identifies and discusses assumptions made for the scientific models and analyses and sources of uncertainty with respect to each endpoint analyzed. Subject to the limitations and assumptions set forth in the analysis, the risk and benefit assessment estimated the net impact of consumption of different amounts of fish. For example, with respect to fetal neurodevelopment, we modeled various “what if” scenarios, in which we estimated what would happen if women of child-bearing age ate more or less fish, or if the amount of methylmercury in the fish they ate were reduced.

The results indicate that consumption of fish species that are low in methylmercury has a significantly greater probability of resulting in a net benefit, as measured by verbal development. The highest net benefit

modeled in our risk and benefit analysis was modest. When we modeled actual baseline consumption for the range of methylmercury concentrations (low to high) the assessment indicated a significant probability of a net adverse effect for 1/10 of 1 percent of children for the central estimate. The highest estimated net adverse effect was also quite modest. For fatal coronary heart disease and stroke, commercial fish baseline consumption is averting a central estimate of over 30,000 deaths per year from coronary heart disease and over 20,000 deaths per year from stroke. The results of our quantitative risk and benefit assessment are generally consistent with research reported in recent years in the scientific literature.

The draft summary of published research identifies primarily secondary analyses of the large body of scientific research on the impact of fish and omega-3 fatty acids on cardiovascular and neurologic endpoints, including research on both prenatal and post-natal exposures. In addition to the IOM report, these secondary analyses include reports by the American Heart Association, the European Food Safety Authority, the International Society for the Study of Fatty Acids and Lipids, the World Health Organization and a previous investigation by FDA. This compendium of research was developed by FDA for use in developing its quantitative risk benefit assessment and provides background for that document. The draft summary of published research identifies and delineates the lines of scientific evidence that indicate the association of fish and omega-3 fatty acid consumption with cardiovascular and neurodevelopmental health outcomes. When available, the compendium of research also identifies reports of quantitative dose-response relationships which may be relevant for risk and benefit assessment modeling. The draft summary of published research describes the context of the overall body of scientific evidence currently available for potential application to the risk and benefit assessment modeling and the draft risk and benefit assessment report.

The agency designated the draft risk and benefit assessment report and the draft summary of published research as a "highly influential scientific assessment" under the Office of Management and Budget's (OMB) Final Information Quality Bulletin for Peer Review (the Bulletin) (70 FR 2664, January 14, 2005). In August 2008, FDA submitted a draft of the risk and benefit assessment report (which at the time also incorporated the draft summary of

published research) to seven scientific experts outside the Federal Government, from a range of scientific disciplines, for purposes of obtaining each expert's independent, written peer review. The draft risk and benefit assessment report and the draft summary of published research that are being made available for public comment reflect revisions made to date in response to the peer reviewers' comments and suggestions. The Information Quality Act Bulletin for Peer Review requires FDA to post at its Web site a report of the peer review that: (1) Contains the names and credentials of the peer reviewers; (2) sets forth the "charge," i.e., the scientific questions asked of the reviewers; (3) provides the verbatim comments submitted by each reviewer (without attribution); and (4) discusses what FDA has done to the documents in response to the peer reviewers' comments. We have posted at our Web site an interim draft of this report that provides this information at <http://www.cfsan.fda.gov/~dms/mehg109.html>, although we expect and plan to finalize this report after revising our draft risk and benefit assessment report and the draft summary of published research, in response to further expert and peer review comments.

Separately, FDA solicited and received comments from scientists at other Federal agencies, including EPA, the National Institutes of Health, the Centers for Disease Control and Prevention, and the National Oceanic and Atmospheric Administration during a review coordinated by OMB. The draft risk and benefit assessment report and the draft summary of published research being made available for comment have been revised to reflect revisions made in response to the inter-agency reviewers' comments.

At the same time we are making these draft documents available for public comment, we plan to provide a revised draft to the original peer reviewers to enable them to submit any further comments. We will revise the draft risk and benefit assessment report and the draft summary of published research as necessary after considering the public comments and any additional comments from the independent peer reviewers. We also plan to provide the revised version of the documents, a summary of the public comments that address significant scientific issues, and the external peer review report to an FDA scientific advisory committee.

After public and advisory committee review of these documents are complete, appropriate risk management actions will then be considered on the basis of currently available scientific

information. The release of these documents for public comment and peer review do not in any way modify the recommendations set forth in the 2004 advisory on fish consumption.

## II. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper 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 Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

## III. Electronic Access

The draft documents described in this notice are available electronically at <http://cfsan.fda.gov/~dms/mehg109.html>.

## IV. Access to Related Documents

All references listed in the reports are available in FDA's Division of Dockets Management (see **ADDRESSES**). Computer programs used in the risk and benefit assessment modeling are available from Clark Carrington, Center for Food Safety and Applied Nutrition (HFS-301), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835, 301-436-1947, e-mail: [Clark.Carrington@fda.hhs.gov](mailto:Clark.Carrington@fda.hhs.gov).

Dated: January 14, 2009.

**Jeffrey Shuren,**

*Associate Commissioner for Policy and Planning.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2008-N-0658]

#### **Risk Assessment of the Public Health Impact From Foodborne *Listeria monocytogenes* in Some Ready-to-Eat Foods Sliced, Prepared, and/or Packaged in Retail Facilities; Request for Comments and for Scientific Data and Information**

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

**ACTION:** Notice; request for comments and for scientific data and information.

**SUMMARY:** The Food and Drug Administration (FDA) is requesting