Peer Review Comments and Responses to a Draft Risk Assessment of the Public Health Effect of an FSIS Catfish Inspection Program

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Office of Public Health Science
Food Safety and Inspection Service
United States Department of Agriculture

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1 INTRODUCTION

This document provides responses to comments provided by five independent peer reviewers to the risk assessment "Draft Quantitative Estimation of the Public Health Impact of an FSIS Catfish Inspection Program" dated April 30th, 2009. The risk assessment estimates the likelihood of foodborne illness and death caused by *Salmonella* and various chemical compounds in or on catfish. This peer review was conducted in a manner consistent with Office of Management and Budget (OMB) Peer Review Guidelines (Final Information Quality Bulletin for Peer Review, December 15, 2004 http://www.whitehouse.gov/omb/memoranda/fy2005/m05-03.pdf).

Reviewers' comments are provided verbatim[1]. Following each paragraph of general comments and specific comments, we provide a response. Responses are in Arial font and indented. All comments and responses are numbered but are not otherwise labeled.

The 2009 FSIS risk assessment for catfish was revised in response to these comments and updated version of this risk assessment has been made available for public comment: http://www.fsis.usda.gov/PDF/Catfish_Risk_Assess_Dec2010.pdf.

2 REVIEWERS

An independent, external peer review of the risk assessment was conducted under contract with ICF International (ICF) in July 2009. Under the OMB peer review guidelines, Agency information submitted for formal peer review is confidential and not to be distributed. Five scientific/technical experts (the primary disciplines/types of expertise needed for review were modeler/engineer, toxicologist, food scientist, and microbiologist) were needed to provide an independent review of the risk assessment. ICF identified and chose potential reviewers. The names of the reviewers were withheld until all five reviews were submitted to FSIS.

Below we present a brief biographical sketch of the reviewers' relevant experience at the time of the review. The numerical order of reviews below is unrelated to the alphabetical listing of names.

[1] Minor formatting changes were made for consistency of presentation.

Douglas John Crawford-Brown, Ph.D.
Dr. Crawford-Brown is Emeritus Professor in Environmental Sciences and Policy and Emeritus Director of the Institute for the Environment, at the University of North Carolina at Chapel Hill. He has also directed the Summer Programme in International Energy Policy and Environmental Assessment in Cambridge, UK, for the past 15 years. He moved permanently to Cambridge, UK, in 2008 and is now Director of Sustainability for Pell Frischmann, an engineering consultancy in London; a Principal in EnviroTech, a business-for-business venture supporting growth of cleantech SMEs; and operates Crawford-Brown Energy and Environmental Consultancy. He received his degrees in physics (BS; MS) and nuclear science (PhD) from the Georgia Institute of Technology. His activities focus on sustainability in the public and private sectors, modeling human health risks from environmental contaminants, modeling alternative policies to tackle environmental problems, assessing the quality of scientific information, and developing tools of risk assessment. He is the author of 140+ scientific articles and 5 books on these subjects. He has served on the USEPA's National Drinking Water Advisory Committee, Clean Air Scientific Advisory Committee, Endocrine Disruptor Screening and Testing Advisory Committee and National Pollution Prevention and Toxics Advisory Committee; on the American Water Works Association's Technical Advisory Workgroup; on the EC's Panel of Scientific Experts on Health and Risk Assessment; on the Legislative Global Climate Change Commission; and on an array of environmental workgroups in the UK, Austria, Mexico, France, Germany and Thailand.

Robert L. Goble, Ph.D.
Dr. Goble is Research Professor in Environmental Science and Policy (ES&P) and Adjunct Professor of Physics at Clark University. He is a member of the George Perkins Marsh Institute, Clark's interdisciplinary research center concerned with human-environment interactions, and was its Director from 2006-2008 . Professor Goble received a B.A. with honors in physics from Swarthmore College in 1962 and a Ph.D. in Physics from the University of Wisconsin in 1967; he worked for nine years thereafter in theoretical high energy particle physics at Minnesota, Yale, Utah, and Montana State. Beginning in 1974 he turned his interests increasingly to technology assessment and hazards, which brought him to Clark University in 1976. Dr. Goble's current research focuses on developing a risk, vulnerability and uncertainty perspective on environmental exposures and health. This has included studies of implications of high uncertainty supported by NSF and WHO and studies of the implications of inter-individual variability among people for assessing exposures and dose response relations supported by the US EPA, the Department of Energy, and by the state of California. Much of this work has been performed with his colleague Dale Hattis at the Marsh Institute and includes studies of the age dependence of exposures and risk.

Dr. Goble is part of a group at Clark developing community based participatory research on health and environmental issues within Worcester; this group is also planning exposure assessments in the National Children's study in Worcester County. Dr. Goble studied risks of extreme sea-level rise for the Stockholm Institute and has studied regional approaches to sustainability for the German state of Baden-Wurttemberg. He was lead author of the exposure volume in EPA's Critical Assessment Document for Acid Deposition. He has worked on projects concerned with the interpretation of fish

consumption data (for the Sierra Club), with vulnerability to mercury exposure (for EPA), and with seafood risk screening (for the Rhode Island Department of Environmental Protection). Dr. Goble has also worked on several projects relating to environmental justice and to cooperation between scientists and non-scientists in risk assessment; these have been supported by the National Institutes for Health and the NSF. Dr. Goble has served on advisory panels for the United Nations, for the National Academy of Sciences, and assisted local community supervision of major health studies. As part of his research Dr. Goble has been a principal mentor of many MA and several Ph.D. students in Physics and in the Environmental Science & Policy Program.

Dariush Mozaffarian, Ph.D.
Dr. Dariush Mozaffarian is a cardiologist and epidemiologist; Co-Director of the Program in Cardiovascular Epidemiology (www.hsph.harvard.edu/research/cvdepi/); Assistant Professor in the Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School; and Assistant Professor in the Department of Epidemiology at the Harvard School of Public Health. His research focuses on the effects of lifestyle, particularly dietary habits, on cardiovascular health and disease.

Dr. Mozaffarian has authored numerous scientific publications and research studies relating to lifestyle and cardiovascular health, including papers on trans fatty acids; fish and omega-3 fatty acids, contaminants, and human health; and the Mediterranean diet. He has served on several national and international committees and advisory boards, including the American Heart Association Epidemiology and Prevention Leadership Committee, Nutrition Committee, Statistics Committee, 2020 Goals Committee, and Trans Fat Initiative Committee; the United Nations Food and Agriculture Organization / World Health Organization Expert Consultation on Fats and Fatty Acids in Human Nutrition; the Pan American Health Organization Task Force on Trans Fat Free Americas; the Canadian Health Measures Survey Expert Advisory Committee; the U.S. Department of Agriculture Seafood Education Project Advisory Group; the Gates Foundation / World Health Organization Global Burden of Diseases Nutrition Expert Group (Chair); and the Reviewer Group for the U.S. Food and Drug Administration Nutrition Methylmercury Risk Assessment.

A Fellow of the American College of Cardiology and Fellow of the American Heart Association, Dr. Mozaffarian received a B.S. in biological sciences from Stanford University (with Honors, with Distinction, Phi Beta Kappa), an M.D. from Columbia University (Alpha Omega Alpha), an M.P.H. from the University of Washington, and a Doctorate in Epidemiology from the Harvard School of Public Health. He is board-certified in Internal Medicine and Cardiovascular Medicine.

Charles R. Santerre, Ph.D.
Dr. Charlie Santerre is a Professor of Food Toxicology in the Department of Foods and Nutrition at Purdue University. Prior to this, he served as an Operations Manager of Chemistry at a private food testing laboratory in Columbus, OH and as an Adjunct Associate Professor in the Environmental Sciences Program at Ohio State University and

as an Assistant Professor in the Environmental Health Science Program and the Institute of Ecology at the University of Georgia. His research involves food toxicology and nutrition. He was the National Spokesperson for the Institute of Food Technologists and has served as Chairperson for the Toxicology and Safety Evaluation Division, and as the Director of the Food Toxicology Center of the National Alliance for Food Safety. He is currently a Scientific Advisor for the American Council on Science and Health, a Scientific Expert for the International Food Information Council, and a full member of the Society of Toxicology. He received a B.S. degree in Human Nutrition and a Ph.D. degree in Environmental Toxicology and Food Science, both from Michigan State University.

Harlee S. Strauss, Ph.D.
Dr. Harlee S. Strauss is an expert in human health risk assessment and toxicology with experience in both community and workplace settings. She has over 20 years of consulting experience and is currently the president of H. Strauss Associates, Inc., a consulting firm she founded in 1988. Dr. Strauss has taught toxicology to undergraduate and graduate students, most recently at Clark University in Worcester, MA.

Dr. Strauss has personally conducted over 60 site specific human health risk assessments several of which had major exposure pathways related to marine or freshwater environments. She has evaluated the toxicity of a range of chemicals including chlorinated and non-chlorinated solvents, petroleum hydrocarbons, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, nitrogen-containing compounds, metals, pesticides, and gases such as hydrogen sulfide. These evaluations were conducted for various purposes including risk assessment, setting or reviewing exposure or clean-up standards, and the investigation of possible relationships between exposure and reported health effects in workers or community residents.

Dr. Strauss has participated in numerous multi-disciplinary projects that applied technical knowledge to challenging problems. She has also been a peer reviewer of toxicology and risk assessment reports, including the Hudson River, the Proposed Bioaccumulation Testing Evaluation Framework for Determining the Suitability of Dredged Material to be Placed at the Historic Area Remediation Site (HARS) in New York, Drake Chemical Incinerator, various screening assessments under the Canadian Environmental Protection Act, and an ATSDR toxicological profile.

3 EVALUATION CRITERIA

Reviewers were asked to respond to the following set of evaluation criteria to facilitate the organization and presentation of their comments. These "evaluation criteria" constitute the FSIS "charge to peer reviewers" (as defined in OMB's Peer Review Guideline, December 2004).

1. Comment on the model documentation.
    1) Is the report clearly written?
    2) Does it completely cover all aspects of the analyses?

3) Does it follow a logical structure and layout?
4) Where data are included/excluded, does the documentation provide adequate justification?
5) If the answer to any of the above questions is No, the reviewer should provide an alternate outline and/or approach for documenting adequately and clearly this risk assessment.

The major assumptions of the model are as follows; please comment according to charge #2 below.

A. Input distribution for each hazard in the analysis.

B. Consumption distribution in the US population

1. Distribution of catfish consumption frequency of each age-sex category.
2. Distribution of the amount of catfish consumed in each age-sex category.

2. Comment on the validity of the model.

a. Are these assumptions logical and adequately justified?
b. Is the selection of data appropriate?
c. Are model outputs reasonable?
d. Is the evaluation of uncertainties sound?

3. Comment on the risk assessment model. As a general matter, comment on the hazards identified in the assessment? Have we failed to identify important hazards? In addition:

a. Chemical Hazards
    i. Are the methods utilized to identify the most significant potential hazards associated with consumption of catfish valid?
    ii. Are the approaches utilized to estimate exposure and level of concern resulting from the consumption of catfish valid?
    iii. Are the approaches utilized to estimate the prevalence of adverse effects (acute and chronic) resulting from hazard exposure valid?
b. Microbial Hazard
    i. Are the methods utilized to identify the most significant potential hazards associated with consumption of catfish valid?
    ii. Are the approaches utilized to estimate exposure and dose-response resulting from the consumption of catfish valid?
    iii. Are the approaches utilized to estimate the prevalence of adverse effects (acute and chronic) resulting from hazard exposure valid?

4 REVIEWER NUMBER 1

Comment 1

1. Comment on the model documentation
    1) Is the report clearly written? yes
    2) Does it completely cover all aspects of the analyses? as well as it can
    3) Does it follow a logical structure and layout? yes
    4) Where data are included/excluded, does the documentation provide adequate justification? no (see comments below)
    5) If the answer to any of the above questions is No, the reviewer should provide an alternate outline and/or approach for documenting adequately and clearly this risk assessment. (see comments below)

The major assumptions of the model are as follows; please comment according to charge #2 below.

A. Input distribution for each hazard in the analysis.
B. Consumption distribution in the US population
    1. Distribution of catfish consumption frequency of each age-sex category.
    2. Distribution of the amount of catfish consumed in each age-sex category.

2. Comment on the validity of the model.
    a. Are these assumptions logical and adequately justified? (see comments below)
    b. Is the selection of data appropriate? (see comments below)
    c. Are model outputs reasonable? (see comments below)
d. Is the evaluation of uncertainties sound? (see comments below)

4. Comment on the risk assessment model. As a general matter, comment on the hazards identified in the assessment? Have we failed to identify important hazards? In addition:
    a. Chemical Hazards
        i. Are the methods utilized to identify the most significant potential hazards associated with consumption of catfish valid? (see comments below)
        ii. Are the approaches utilized to estimate exposure and level of concern resulting from the consumption of catfish valid? (see comments below)
        iii. Are the approaches utilized to estimate the prevalence of adverse effects (acute and chronic) resulting from hazard exposure valid? (see comments below)
    b. Microbial Hazard
        i. Are the methods utilized to identify the most significant potential hazards associated with consumption of catfish valid?
        ii. Are the approaches utilized to estimate exposure and dose-response resulting from the consumption of catfish valid?

iii. Are the approaches utilized to estimate the prevalence of adverse effects (acute and chronic) resulting from hazard exposure valid?

In addition, I was specifically asked to address the following:

1. Answers to charge questions and any additional comments
2. A description of the procedures used to arrive at your recommendations (Please make clear and substantiate the methods and considerations upon which your recommendations are based.)
3. A summary of your findings; and
4. A list of sources relied upon (references).

Since I am a food scientist/toxicologist, I will focus on the chemical safety portion of the Draft.

Overall Rating: The risk assessment is well written and all aspects are clearly defined and explained. The length of the document is appropriate.

Concerns: Since the purpose of this risk assessment was to determine the positive impact of a continuous 'catfish' inspection system on catfish producers/processors in regards to public health, I will address the practical aspects of the risk assessment.

This type of approach may work well for pathogens which are likely to be present in the gut of all catfish but I believe that there are significant problems in assessing contaminants in the same manner. I would like to first address domestically-grown catfish since this is where I am most experienced. Let me start with a discussion of some compounds that are not <u>intentionally</u> added to catfish feed or production ponds.

Mercury – This is a non-point source environmental pollutant that is found in all fish. It primarily enters through the diet and binds to proteins in the muscle. It also concentrates in organs, like the kidneys, brain and liver, but consumers do not generally consume these parts of the catfish. Mercury accumulates in large marine fish species and is not reduced by cooking. Our studies have shown that the average mercury concentration in domestically-produced catfish fillets was ~8 ppb with a maximum of 89 ppb. The FDA regulatory limit for fish is 1,000 ppb. The EPA's Reference Dose (RfD = 0.1 µg/Kg body weight/d) is significantly more conservative but it would allow a 60 Kg pregnant or nursing woman to eat up to 6 µg Hg/d or 750 g (1.6 lb) of catfish per day. While the is intense scientific debate about the findings from studies conducted in the Seychelle Islands vs. Farao Islands, the National Research Council (2000) found adequate evidence for development and implementation of the EPA's RfD. Thus, for sensitive populations, it is best to use the EPA's RfD instead of the ATSDR's MRL in order to be more protective of the fetus and nursing infant. The risks to the fetus and nursing infant are believed to far outweigh the risks to the general population. So, this should be considered when developing a risk assessment. Regardless of one's position of the safety limit, mercury concentrations in catfish are already well below regulatory limits for commercial seafood and it would be difficult to further lower these concentrations. Thus, the benefits from lowering mercury residues would have a marginal impact on risk and an inspection

system which monitors mercury in domestic catfish would provide no benefits. To counter the potential adverse IQ effects that have been associated with elevated intakes of mercury, it might be better to require the inclusion of fish oil which contains long chain omega-3 fatty acids (EPA, eicospentanoic acid; DHA, docosahexanoic acid) into the catfish feed. The beneficial impact to public health would outweigh the predicted beneficial impact of an inspection system. Unfortunately, increasing fish oil in catfish feed would also increase PCB concentrations.

Response 1

The initial draft risk assessment's predictions regarding adverse human health outcomes associated with mercury (and other chemical compounds) were determined to be insufficient to warrant inclusion in the cost-benefit calculations of the regulatory impact analysis. In particular, there is no empirical data that measures the level of effectiveness of an FSIS inspection program to reduce chemical residues on food. The revised risk assessment now focuses only on the microbial hazard *Salmonella*, with which estimates program effectiveness can be based on FSIS empirical data on poultry models. The appendix of the revised risk assessment includes the hazard identification and exposure assessment sections for the chemical hazards. Including these sections provide a qualitative assessment of these hazards.

Comment 2

Lead – I am concerned that data regarding lead concentrations in catfish tissue may be dated. Since the elimination of leaded gasoline, the concentrations of lead in all food products have significantly declined. The data reported in our catfish study are now 15 years old. Thus, lead is likely to be less of a public health concern today in regards to exposure from food.

Response 2

The data the reviewer is referring to are still the most recent quantitative data for lead in catfish. As such, these data were chosen for use in the original version of the catfish risk assessment. However, because the revised risk assessment focuses on *Salmonella*, the effects of lead (and other chemical compounds) are no longer considered.

Comment 3

Diuron – Unlike pathogens and mercury, this pesticide behaves like a point-source pollutant and is more likely to show up only in catfish grown near rice-production areas, like the Mississippi delta. Since it is a not a volatile or semi-volatile compound, it must be measured using a single residue method. I am not aware of any diuron residue data for catfish but I would bet it is somewhat limited. This would be one example where testing for diuron in catfish that were produced in Georgia, for instance, would not provide meaningful results. To assess exposure to diuron, one needs residue data and also data involving the consumption of the contaminated catfish. So, the risk to the entire population might suggest that this contaminant should not be included in a risk

assessment. However, the risk to a specific population (i.e., those that eat catfish produced in this region of the country) may suggest that diuron be included in the assessment. My intention here is not to advocate that diuron be included but rather to point out a limitation of this risk assessment.

Response 3

Diuron and other herbicides were considered medium priority hazards following the hazard identification stage of the original version of the risk assessment. Because the revised risk assessment focuses on *Salmonella*, the effects of diuron (and other chemical compounds) are no longer considered.

Comment 4

PCBs/Dioxins/Furans – Dioxins are highly toxic compounds that have found their way into domestic catfish from feed. Once they were detected and the source identified, it was straight forward to remove them from feed and eliminate the problem. Unfortunately, a congener analysis is expensive and can cost $1,400 per sample. In addition, the assay may take several weeks to complete which make it impractical for use in an inspection system. I am not aware of a rapid assay for dioxins in fish tissue; however, USGS has developed a sample preparation method that uses a commercially-available ELISA (enzyme-linked immunosorbent assay) kit to measure PCBs as Aroclor. We have evolved their method to make it useful for screening recreationally-caught fish when developing fish consumption advisories. The assay can be completed in a matter of hours but confirmation with a GC/MS method would be recommended. While PCBs are still percolating from landfills and Superfund sites, their presence in the environment or around production ponds can be determined and the need for further testing minimized. More typically, PCBs and dioxins enter catfish through contaminated feed and here is where it would be best to monitor for PCBs/dioxins/furans. If PCB concentrations in catfish are below the federal tolerance of 2 ppm, then it is questionable whether an inspection program will be useful. If a limit were established for PCB concentrations in feed, then the concentration in catfish could be lowered.

Response 4

As mentioned (Response 3) the national residue sampling program will determine the chemical compounds to target each year. Testing methods will also be determined using this interagency process.

The Food and Drug Administration has the statutory authority to set tolerances for chemicals in feed.

Comment 5

DDT/Organochlorines – Even though many of these pesticides were banned in the U.S. during the mid-1970s, residues can still be detected in many meat, poultry and seafood products. The regulatory limit for DDT-like compounds is 5 ppm and very few domestic catfish even come close to this concentration. Our catfish study found mean DDT in those samples that had detectable amounts (55%) to be 43 ppb. There are some hot-spots of chlordane around the country. Here again, for domestic catfish, measuring pesticides

that have long since been banned may not be the best use of resources and may provide little benefit to public health.

Response 5

The risk below regulatory limits is not zero. The sum of low level risks across an entire population may be significant. Because the revised risk assessment focuses on *Salmonella*, the effects of DDT (and other chemical compounds) are no longer considered.

Comment 6

For the previously mentioned compounds, a continuous inspection program would be of little value since these compounds are present at concentrations that are well below regulatory limits. It might be helpful to occasionally monitor some of these compounds in feed since the diet is the primary route of exposure. One other metal that was not mentioned in the Draft is chromium which may be found as an environmental pollutant near wood treating facilities that can be in close proximity to production ponds. Another class of compounds which is being detected in fish collected across the country is the brominated flame retardants (polybrominated biphenyl ethers). These compounds are increasing being detected in wild fish but concentrations are relatively low. A couple of the commercial PBDE formulations have been banned or voluntarily withdrawn by the manufacturer.

Response 6

As mentioned (Response 1) the national residue sampling program will determine the chemical compounds to target each year. It is unlikely that FSIS inspection programs would generate sufficient benefits to warrant inclusion of this compound in the risk assessment. The Food and Drug Administration has the statute authority to set tolerances for chemicals in feed.

Comment 7

I recommend that environmental pollutants (i.e., mercury, PCBs, lead, DDT) which are not intentionally added and which are below regulatory limits be eliminated from the risk assessment. I also suggest that some context be provided for use of cancer as an endpoint. It is difficult to compare illnesses from a foodborne pathogen to lifetime risk to cancer.

Response 7

We agree with the reviewer that comparison of numbers of illnesses to numbers of cancers is difficult. Yet, economic analysis is intended to provide such comparisons. Using our original risk assessment predictions, the economic benefits of foregone cancer cases were not considered substantial. Therefore, compounds associated with cancer risk are not considered further in the revised risk assessment.

Comment 8

Let me discuss some of the chemicals that may be intentionally added to feed or production ponds. In our study (and also from FDA's monitoring program), the pesticide chlorpyrifos, was detected in catfish samples from MS and TX during the first year of our study. There was concern that the pesticide was entering ponds from aerial drift during application to adjacent row crops and it was subsequently banned from use in these fish production areas. Since catfish are more tolerant to this pesticide than many other fish species, some have surmised that this pesticide was being intentionally added to ponds to kill scrap fish just prior to harvest (i.e., a harvest aid). Our research never attempted to determine whether chlorpyrifos was entering through intentional or unintentional means. However, we did develop a rapid method using a commercial ELISA kit to measure this compound in fish tissue. It was our belief that if producers were aware that a screening method was being used, any possibility of improper use would disappear. To our knowledge, this kit has never been used by processors. Following the controversy involving chlorpyrifos, I have heard comments that 2 other compounds (diazinon and malathion) had replaced chlorpyrifos and were being used (illegally) as a harvest aid. I have no evidence that would support or refute this contention. It may be prudent to monitor these pesticides to discourage improper use during catfish production.

Response 8

This comment pertains to the national residue sampling program. As already mentioned (Response 1) this program will determine which chemicals to include in a residue surveillance program. Chemicals selected for testing within the National Residue Program scheduled sampling program are ranked using several factors including regulatory concern, violation data, etc.

Comment 9

Drugs – One drug (emamectin) is being used in salmon production by every foreign salmon producing country. This chemical, which is added to feed and used to treat for sea lice, is being legally used in the U.S. under an IND but it has not yet been approved for general use. While it appears that approval is imminent, other countries (Canada, Chile, Norway) have disregarded U.S. policies by using this drug in salmon that are exported to the U.S. FDA-CVM is not currently testing for emamectin in imported or domestic salmon. If producers follow an approved withdrawal time, the residues of certain antibiotics can be at or below detection limits at harvest. For the current risk assessment, we should consider whether enforcing residue restrictions would benefit consumers even if there are indirect benefits. To illustrate, it is thought that excessive use of 'agricultural grade' emamectin in Chile has led to resistance by sea lice and has increased the spread of infectious salmon anemia. As a result of ISA spread, many production areas have been shut down. The local affect is that domestic consumers may find it to be increasingly difficulty to purchase farmed salmon. Since Chile provides about 60% of the salmon consumed in the U.S., any reduction in their exports to the U.S. may reduce our dietary intake of omega-3 fatty acids and thereby, increase the risk of sudden cardiac deaths. So in this scenario, properly enforcing regulatory limits can improve public health.

Response 9

It is unclear from this comment whether emamectin is used in the catfish industry. We agree with the comment "properly enforcing regulatory limits can improve public health". The national residue sampling plan (see Response 1) will determine the compounds to target each year.

Comment 10

Listeria monocytogenes – Since there is a growing effort to encourage pregnant women to eat fish in order to have healthy babies, I would suggest that the risk assessment looking more closely at the risks from this pathogen which can cause spontaneous abortion and can grow at refrigeration temperatures. Seafood, including catfish, can be improperly cooked by consumers.

Response 10

Hazard identification determined that *Listeria monocytogenes* was a medium priority microbial hazard. This and other foodborne agents associated with the consumption of catfish are discussed in a recently published scientific paper (McCoy, E, Morrison, J., Cook, V., Johnston, J., Eblen, D., and Guo, C. (2011). Foodborne Agents Associated with the Consumption of Aquaculture Catfish. *Journal of Food Protection* 74(3): 500-516(17)). Catfish are rarely produced in a ready-to-eat (RTE) form and human *Listeria monocytogenes* foodborne illnesses are most commonly associated with RTE products. Furthermore, the estimated total number of annual *Listeria monocytogenes* illnesses among the U.S. population is about 1,662 cases (Scallan, E., Hoekstra, R. M., Angulo, F. J., Tauxe, R., Widdowson, M., Roy, S. L., Jones, J. L., and Griffin, P. M. (2011). Foodborne Illness Acquired in the United States – Major Pathogens. *Emerging and Infectious Diseases* 17(1): 7-15). There is no evidence to suggest that catfish are more likely than other meat products to be contaminated with *Listeria monocytogenes.* Because the total servings of catfish consumed annually are substantially smaller than other meat products, it is unlikely that many *Listeria monocytogenes* illnesses would be attributed to catfish in our baseline scenario. If there are few baseline cases associated with catfish, then the cases avoided by the FSIS inspection program will be less significant.

Comment 11

One common difficulty that is encountered when developing a risk assessment regarding chemical contaminants is the lack of comprehensive studies that measure residue concentrations. It is often difficult for investigators to obtain research funding that would allow collection of food residue data. This is a limitation that poses a significant negative effect on the quality of this assessment. An accurate risk assessment requires adequate data to assess exposure and properly estimate human risk from this exposure. For chemicals that have not been approved for use in aquaculture production and processing (i.e., melamine, malachite green), there are significant gaps in residue data and there are

also inadequate estimates of human risk. Ideally, a risk assessment will lead to a risk management plan which should include: routine testing for known and unexpected chemicals in feed, fish and water; an effort to develop analytical methods; and an educational component to help producers and processors make better decisions.

Response 11

The focus is on predicting the effectiveness of a continuous inspection system in reducing human exposures/illnesses to microbial and/or chemical hazards. We strongly agree with the comment that comprehensive studies are most useful for risk management.

Comment 12

In conclusion, due to the: lack of sufficient or current residue data; lack of consumption and exposure data that pertains specifically to sensitive populations (pregnant or nursing women) or consumers that are regionally exposed to a selected contaminant; lack of human studies that quantify the risk from to exposure to selected hazards; and lack of differentiation between background pollutants and illegal/intentional additives, this risk assessment cannot adequately determine the benefits of a continuous inspection program. I would therefore have to disagree with the conclusion as stated, "Our analyses indicate that the implementation of an FSIS inspection based program will have a beneficial public health impact by decreasing the number of such adverse effects experienced by US consumers." I do believe that the limitations as stated should not reflect negatively on the authors that developed this excellent document.

Response 12

The revised assessment, which focuses on Salmonella, better validates the output estimates with more detailed discussion of the uncertainty surrounding the effectiveness of the FSIS inspection program. The revised risk assessment no longer considers the effects of chemical compounds.

5 REVIEWER NUMBER 2

Comment 13

2. Comment on the model documentation

1) **Is the report clearly written?**

This report appears to have been written by folks with expertise in modeling, but little understanding of the underlying subjects of toxicology and the factors that determine chemical exposure-dose from fish consumption. It is well organized, but it is very short on explanation and detailed documentation of datasets actually used. For example, the written report does not provide the datasets for chemical contamination used in the model. While the data may be in the Excel spreadsheets sent to reviewers, these were clearly not made for public consumption and not adequately labeled, described and/or documented for outside review. For other parameters, such as toxicity, meal size and cooking loss, the report does not describe any of the extensive datasets available, but

instead relies on one paper or website as the basis of the evaluation without regard to the many other papers in the literature that may show alternate relationships or values for the necessary parameters for the modeling. The report gives virtually no documentation for the reasons underlying the selection of distributions, only the final result. Curve-fitting (hazard concentrations, pareto distribution) is not a good reason to use a distribution if other distributions have an underlying physical or biological basis.

Response 13

The revised risk assessment is focused on predictions related to *Salmonella*. This update provides a more detailed description on the *Salmonella* model inputs than the original version (which necessarily was brief when fully discussing all 11 hazards). The remaining 10 hazards are included in the appendix of the revised risk assessment.

Comment 14

The report lacks perspective of what is important and how the different parts of the assessment connect with each other. For example, the report makes extensive use of detailed datasets (e.g. cardiovascular effects of lead) without considering whether the other parts of the analysis (i.e. the exposure assessment) are adequately robust to support that detailed an evaluation (I don't believe it is). In addition, it ignores the fact that other chemical hazards, such as the chlorpyifos, an organophosphate pesticide, have cardiovascular effects that could contribute to the risk, but don't have the detailed age/sex breakdown. The report doesn't consider the toxic endpoints that have been associated with PCBs and DDT in wild caught fish (neurodevelopmental effects, reproductive effects – both perhaps ultimately stemming from endocrine disruptor activity), even though these chemicals are included in the identified hazards. The report neglects issues of ethnicity, which is an important determinant of exposure in terms of parts of fish consumed, method of preparation, and perhaps frequency of fish consumption.

Response 14

As indicated by the reviewer, there are numerous adverse effects associated with exposure to environmental chemicals. However, the nature of the adverse effects estimated in this risk assessment was limited to effects to which dose vs. response functions could be ascertained.

Catfish consumption data were derived from 1996-2006 NHANES surveys. It appears that ethnicity is not included in these data sets. The assessment is based on the consumption of fillet muscle which constitutes the majority of catfish consumed in the US. Method of preparation (breaded vs. non-breaded, cooking style) was included in the risk assessment.

Comment 15

The report goes to great effort to develop a probabilistic model of adverse outcomes, but does not present the ranges of results obtained with the exception of one graph for *Salmonella* illness avoided and one graph of cancer avoided. Instead, the results are summarized as point estimates in Table 9 with no sense of the distribution or even a comment on where the number falls in the distribution or what the distribution looks like. If the probabilistic approach is pursued, there should be graphs of distributions of the risk results for the individual scenarios as well as the risk avoided.

Response 15

The graphs presented for *Salmonella* and cancer were included for illustration of the annual variability in cases. As a default we assumed our predictions (which were based on probabilistic models) were rates from a Poisson process. This assumption was explained in the report. Providing graphs for all outcomes was considered, but we decided that two illustrative graphs would be sufficient. If the comment refers to uncertainty, then we provide the range of uncertainty in Table 11.

The revised risk assessment is focused on *Salmonella*, and the results are presented in greater detail.

Comment 16

2) Does it completely cover all aspects of the analyses?

Almost all aspects of the analyses should explained in more detail, as discussed in the responses below.

3) Does it follow a logical structure and layout? Yes.
4) Where data are included/excluded, does the documentation provide adequate justification? No. See response under hazard identification.
5) If the answer to any of the above questions is No, the reviewer should provide an alternate outline and/or approach for documenting adequately and clearly this risk assessment. See subsequent comments.

The major assumptions of the model are as follows; please comment according to charge #2 below.

A. Input distribution for each hazard in the analysis.

Hazard concentration in fish: The Pareto distribution is used for the hazard concentration. A log-normal distribution is used for this distribution for most environmental datasets with which I am familiar. There should be some discussion of why a log normal distribution was not utilized and the difference in outcome had it been used instead of the Pareto distribution (sensitivity analysis). There is no discussion of the uncertainty of the choice of distribution anywhere in the report. Moreover, the report does not provide the underlying data of the hazard concentrations in fish. The data for the inorganic (metal) hazards appear to come from Santerre et al. 2001 which reports the mean, maximum and standard deviation of the detects along with the limit of detection and the number and

percent of detects. Normal and lognormal distributions could be determined from these data. It is not the case, as stated in the text, that the Pareto distribution optimally described the dataset as it appears that the authors of this report did not use the original dataset, only the summary of the dataset provided in the cited published paper.

Response 16

The justification for the Pareto distribution was informal; it was a conservative choice (because it places more probability in the right-hand tail than a lognormal distribution) and was straightforward to adapt to expert opinion about the true distribution of contamination among catfish. Given the variable (and sometimes very limited) data available, a heuristic approach was considered simpler to apply across multiple hazards versus a formal analytic approach applied to each hazard.

The revised risk assessment is focused on *Salmonella*. Its descriptions of inputs are more detailed than the original risk assessment.

Comment 17

A. Consumption distribution in the US population

I think the methodology used to determine catfish consumption (frequency, meal size, number of consumers) is weak, or at a minimum needs far more clarification. The authors seemed to equate catfish production data with catfish consumption data. However, there is obviously some factor of wastage, which is likely well known in the industry. In addition, it was not specified whether catfish production was whole fish or fillets. Since catfish are sold in many forms including whole eviscerated fish, the production data is likely more than the weight of fillets.

Response 17

We agree with the comment. The updated risk assessment uses data that better represent the amount of catfish consumed in the United States each year [U.S. Centers for Disease Control and Prevention (CDC). National Health and Nutrition Examination Survey, retrieved from http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm; and U.S. Department of Agriculture, National Agricultural Statistics Service (NASS), 2009, Catfish Processing. Retrieved from http://usda.mannlib.cornell.edu/usda/nass/CatfProc//2000s/2009/CatfProc-02-18-2009.pdf]. One notable change in the consumption calculations is the use of the processed weight of catfish instead of the catfish weight prior to processing.

Comment 18

The use of NHANES reports of catfish consumption is more likely an underestimate than an overestimate of the number of catfish consumers. Many folks who eat not-self-caught

fish have no idea what kind of fish they are consuming. This is particularly true for fried fish when they are not the preparers. Who would know if the fish and chips you ordered at a restaurant was catfish?

Response 18

Queries were made to university, industry, and government organizations regarding sources of catfish consumption data. Through this process, the 1996-2006 NHANES data were identified to be the most extensive catfish consumption data. Estimates of total U.S. catfish consumption were based on National Marine Fisheries Service and National Agricultural Statistics Service data.

Comment 19

It is not clear to me why the authors did not include catfish consumption estimates from the USDA Continuing Survey of Food Intake by Individuals (CSFII). For example, the EPA Exposure Factors Handbook (1997) cites CSFII 1989-1991 for mean per capita intake of catfish, as consumed, of 1 g/person/day and uncooked of 1.38 g/person/day. The mean and distribution of values for catfish consumers is the most relevant data, and perhaps could be determined from this dataset. Subsequent EPA analyses have total finfish values that can serve as upper bounds of estimates, although farm raised finfish seem to be included in the survey questions (c.f., EPA 2007, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=132173) and would be a better upper bound value. Yet another option for determining catfish consumption would be the use of industry data. There should also be a discussion as to whether or not farmed catfish consumption is increasing or decreasing (I believe it is increasing), and make some allowance for this in the assessment.

Response 19

We are familiar with the Continuing Survey of Food Intakes by Individuals (CSFII) consumption surveys and have used them in many past quantitative risk assessments as part of our exposure assessment. Since 2002, the CSFII and NHANES consumption data have been integrated into a more current national consumption survey. The 1996-2006 NHANES data sets currently used in this risk assessment represents the integrated data of the two consumption surveys.

Comment 20

1. **Distribution of catfish consumption frequency of each age-sex category.**

I don't understand why there are so many age/sex categories. The consumption data aren't good enough to support this many categories, or at least it is not documented in the report. Calculations based on these estimates are only as reliable as the least reliable data, which is the great uncertainty of the consumption data.

Response 20

All age/sex categories contain approximately the same number of survey respondents. Segregating the consumption data into these groups was aimed at minimizing the probability of neglecting consumers whose consumption patterns deviate significantly from the mean.

Comment 21

1. **Distribution of the amount of catfish consumed in each age-sex category.**

This is not well explained and documented.

2. Comment on the validity of the model.

a. **Are these assumptions logical and adequately justified?**

The model assumes that only catfish fillets, or meat derived from the fillet, are consumed by the US population. I don't believe this is correct based on the products described in this report: http://srac.tamu.edu/tmppdfs/453908-184fs.pdf?CFID=453908&CFTOKEN=47605949&jsessionid=90305fea38ece0c3b0102c642a6b51653753

Consumption of fish parts other than fillet (parts that have a higher fat content) could lead to higher concentrations of organic contaminants, such as PCBs and DDT, although it may not make a difference to the inorganic hazards. The fillet-only assumption could lead to a substantial underestimate of exposure for certain subpopulations, as there are ethnic preferences to parts of fish consumed and preparation methods. For wild caught catfish, Weintraub and Birnbaum (2008) suggest that parts of fish consumed partially accounts for the higher PCB body burdens of non-Hispanic Blacks. http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1021&context=usepapapers

Response 21

The great majority of catfish residue data were generated from the analysis of the fillet tissues. To estimate risk associated with consumption of other catfish tissues would necessitate the acquisition of additional residue data for these tissues, which was unavailable at the time that this risk assessment was conducted.

Wild caught catfish falls outside of the scope of this risk assessment and was therefore not considered. As discussed elsewhere, the chemical residue analysis is no longer a focus of the revised risk assessment.

Comment 22

Equation 3:

The reason for the inclusion of the term I(h,y), the indicator of whether or not a catfish fillet is contaminated by a particular hazard, is not clear to me. If the concentration distribution X(h,y) includes the non-detected values, then the I(h,y) term should not be

necessary. Its inclusion should lead to an underestimate of predicted risk. If the I(h,y) term is needed because of the choice of a Pareto distribution means that only detected concentrations are included in the X term, then that should be stated. However, as noted previously, there should be a sensitivity analysis showing the difference in outcome of this input distribution/model vs. the more commonly used log-normal distribution for the concentration term.

The cooking term Ci should include a term for cooking type. Additional preparation methods should be included, including soups which have no loss of chemical contaminants (hazard) as a result of preparation.

Response 22

The revised risk assessment focuses solely on *Salmonella*. That pathogen does not rely on a Pareto distribution assumption.

Comment 23

Toxicity evaluation

I am extremely uncomfortable with the approach used to determine toxicity throughout this report. There is an attempt to incorporate probabilistic approaches to the assessing toxicity. However, these approaches are not approved by the USEPA nor are they widely used or agreed upon in the scientific community. There is not nearly enough detail provided in this assessment to pioneer new methods of toxicity evaluation and I have no confidence in the reliability of the outcome.

Response 23

Probabilistic risk assessment approaches are widely used throughout the international risk assessment community, especially in the area of food safety. The approaches used in this assessment received favorable response from reviewers in EPA's office of pesticide programs.

A search of Monte Carlo on the EPA website generated many references to EPA's support of this technique. For example:

A Monte-Carlo assessment provides a probabilistic or statistical assessment *of dietary risk, using more refined information than is used in the Dietary Risk Evaluation System calculation. With the advent of Monte-Carlo and probabilistic techniques, it becomes possible to estimate more accurately the complete distribution of exposures to the entire population.*

Rather than the crude "high end,"single- point estimates, Monte-Carlo provides better, more accurate information on the range and probability of possible exposure and their associated risk values. (http://www.epa.gov/oppfead1/trac/trac3.htm)

The intended goal of the two draft white papers, *Using Probabilistic Methods to Enhance the Role of Risk Analysis in Decision-Making, With Case Study Examples*, and *Using Probabilistic Methods to Enhance the Role of Risk Analysis in Decision Making - Managers' Summary* is to describe potential and actual uses of probabilistic tools in the risk decision process, and to encourage their further implementation in human,

ecological and environmental risk analysis and related decision making at EPA. The enhanced use of probabilistic analyses to characterize uncertainty in assessments would not only reflect external scientific advice on how to further advance EPA risk assessment science, but will also help to address specific challenges faced by managers and improve confidence in Agency decisions (http://www.epa.gov/osa/raf/prawhitepaper/index.htm).

Further information on EPA's endorsement of probabilistic approaches for risk assessment can be viewed at:

Guiding Principles for Monte Carlo Analysis (http://www.epa.gov/NCEA/pdfs/montcarl.pdf)

Using Probabilistic Methods to Enhance the Role of Risk Analysis in Decision Making with Case Study Examples (http://www.epa.gov/osa/raf/prawhitepaper/pdf/pra_wp_draft_0609.pdf)

Comment 24

For the cancer risk assessment, the model equations/values in the spreadsheet did not match the derivation of the EPA toxicity factor. The cancer slope factors developed by EPA are calculated based on an assumed 70 year lifetime. Since this fixed value is incorporated into the value of slope factor, it is not appropriate to use probabilistic methods to determine a lifetime, which on average was 82 (according to the spreadsheet). This has the impact of reducing the cancer risk by a factor of 70/82 based only on incompatible uses of point and probabilistic methods.

Response 24

The reviewer's comment is logical, however, the revised risk assessment focuses only on the potential effects of *Salmonella* contamination.

Comment 25

For PCBs, a slope factor of 2 (mg/kg-d)-1 is most often used in risk assessments involving food chain consumption. A value of 1 (mg/kg-d)-1 was used in this assessment, with no discussion of how it would change the result. The text does not give any basis for assessing this independently as it doesn't give the cancer risk by chemical hazard, only aggregated numbers.

Response 25

The slope used in this risk assessment was obtained from the USEPA IRIS website. The use of a slope of 2 (as suggested by the reviewer) would lead to a reduced estimate of PCB associated carcinogenicity. Since the use of a slope value of 1 did not lead to a significant estimate of

PCB related cancers, using a slope of 2 would likely lead to the same result.

Note: the revised risk assessment focuses only on potential adverse effects associated with *Salmonella*.

Comment 26

For the non-cancer probability, the authors base their approach on a paper published over a decade ago by Price et al. The highly reputable authors of this paper provide some examples of a proposed methodology. However, it is controversial among at least some regulators, and it has not been used in the EPA regulatory community. Moreover, the parameters within the paper, for example the form of the uncertainty factors and the parameters used to describe the distributions, have not been validated. Indeed, the work of Dale Hattis and his colleagues on the amount of variability among humans for individual endpoints should play a huge role in any development of uncertainty factor distribution used for regulatory and other purposes. This variability is far greater than that used in this modeling exercise. None of this uncertainty was even mentioned in the document under review.

Response 26

FSIS will revisit this issue should it further consider risk estimates for non-cancer endpoints for chemical hazards. The revised risk assessment focuses on *Salmonella*, and the effects of chemical compounds are no longer considered.

The revised catfish risk assessment uses the World Health Organization *Salmonella* dose-response model.

Comment 27

The method for the estimation of the blood concentration of mercury appears to be deterministic, based on the text. If it was probabilistic, the range of values and the distribution utilized should be stated in the text. If it was deterministic, then there should be some kind of bounding estimates as there will be substantial variability in all of the parameters.

For lead, the authors should consider using the EPA lead model to estimate the additional lead burden in adults and children. This model incorporates background and pharmacokinetic data and will give a more reliable estimate of blood lead concentrations. However, before it is used, the exposure parameters need to be reassessed including meal size and cooking loss (see below).

Response 27

FSIS will revisit this issue should it further consider risk estimates for non-cancer endpoints for chemical hazards. The revised risk assessment focuses on *Salmonella*, and the effects of chemical compounds are no longer considered..

Comment 28

b. **Is the selection of data appropriate?**

Use of animal LD50s
Acute toxicity mortality evaluations were based on animal LD50 studies with the application of uncertainty factors. However, there are very good human data on the acute toxicity for several of the identified chemical hazards, and these should be used instead of animal LD50s. For example, the acute toxicity of chlorpyrifos (an organophosphate) has been reviewed as part of the EPA reregistration process. A review panel summary of acute effects can be found at http://docserver.ingentaconnect.com/deliver/connect/tandf/10937404/v2n4/s2.pdf?expires=1246894648&id=51079748&titleid=333&accname=Guest+User&checksum=02D01554EF2788963EDC7682ADEEED7A

Response 28

We agree that human data are preferable to animal data as inputs for human risk assessments. However, the revised risk assessment focuses on *Salmonella* and does not use animal LD50s.

Comment 29

Meal size:
I believe the distribution used to estimate meal size is too narrow. The triangle distribution used (for *Salmonella*) is limited to a 7-11 oz fillet, referenced to a particular website. However, other websites show the availability of fillets sizes of 2-3 oz, 3-5 oz, 5-7 oz etc. The recipes on the Epicurious website call for 5-7 oz fillets. A USDA publication described 3.5 oz servings, http://srac.tamu.edu/tmppdfs/453908-501fs.pdf?CFID=453908&CFTOKEN=47605949&jsessionid=90305fea38ece0c3b0102c642a6b5165375. The 3.5 oz value seems to be the mean serving size used for the catfish consumption in section 4.3 for calculating the number of meals/year for a catfish consumer. The inconsistency in meal size should be resolved or at least explained. The methodology that underlies the determination of meal size needs to be more clearly spelled out.
An alternate method for meal size is to look at the many surveys and the industry literature that describe meal size. In general, the meal sizes reflect uncooked fish. I don't understand the rationale for reducing meal size because of breading. People won't choose smaller fillets. It seems to be an arbitrary correction.

Response 29

This has been corrected in the revised risk assessment. An excerpt from the revised report,

> *The mean serving size determined from the 8-year dataset analysis was 122.28 grams per eating occasion. Given the low frequency of catfish consumption, this analysis assumed the quantity consumed in one day represented a single catfish serving. The serving size*

random variable ranges from 5 grams to over 500 grams (1st and 99th percentiles)(Figure 5). . This random variable is modeled as an empiric distribution because attempts to fit the data to parametric distributions did not demonstrate adequate goodness of fit.

The estimates for fraction baked and fraction breaded were taken from both the one and two day datasets as independent estimates using the SUDAAN CROSSTAB procedure and averaged. Six catfish food codes were used to ascertain the fraction baked (versus fried) and the fraction breaded as proportions of the weighted US population catfish consumer estimates. The population-adjusted estimates were $f_{Bread} = 0.79$ *and* $f_{Baked} = 0.24$*. Breading is assumed to represent between 20% and 30% of total serving weight. Therefore, serving size for breaded servings is multiplied by a randomly selected value between 0.7 and 0.8 (i.e.,* $Bread\_effect = Uniform(0.7, 0.8)$*) to adjust for the amount of catfish in such servings.*

Comment 30

Cooking method and Cooking loss (chemical):
The model only allows for baking and frying. However, there are recipes for other preparations, including use in soups (SRAC publication above) for which there would be zero cooking loss. This should be included in the model.

Response 30

Frying and baking constituted virtually all (>99%) of the survey respondents and were therefore the methods considered in this risk assessment

Comment 31

The sources of the cooking loss values and the rationale underlying the use of a normal distribution (rather than, for example, a log-normal distribution or a triangle distribution) are not clear to me, nor are they described in the document. I looked at the underlying reference for cooking loss from arsenic, cadmium, mercury and lead. They reported the results in raw and cooked, both wet weight, thus any cooking loss (gain) could be just due to moisture differences. In addition, the text clearly stated that none of the losses were statistically significant. Thus, I believe it is inappropriate to incorporate any cooking loss for metals. The cooking loss for lead needs particularly careful attention as the sensitivity analysis indicated that the final output for IQ was quite sensitive to cooking loss. Presumably this would also be the case for the cardiovascular effects that are only based on lead, although those results are not presented in the report.

Response 31

Since serving size estimates are based on consumption of cooked products, cooking-associated changes in hazard concentrations (even if

such changes are associated with cooking-induced moisture changes) should be incorporated into the model.

Sensitivity analysis suggests moderate elasticity for IQ effect (arsenic, cadmium, lead, mercury), none for CV effects, and extremely inelastic effects for cancer (DDT, PCB, and metals). Therefore, for most catfish associated chemical hazards, the cooking losses appear to be minimal.

Additionally, the revised risk assessment focuses only on the public health effects from *Salmonella* contamination.

Comment 32

The referenced cooking-loss data for PCBs (Bayen 2005) came from experiments using salmon. This paper also reported on DDTs. Salmon is a fatty fish while catfish are not. One would expect greater PCB cooking losses from salmon than from catfish as the loss is associated with the loss of fat (this is stated in the Bayen 2005 article as well as many others). More details regarding cooking methods and cooking losses should be addressed in both the text and in an uncertainty analysis. Cooking loss for PCBs for both point and Monte Carlo analyses were described in detail in the EPA Risk Assessment for the Housatonic River, Rest of River, fish consumption:
http://www.epa.gov/NE/ge/thesite/restofriver/reports/hhra_219190/219190_HHRA_Vol4_FW.pdf
This report also takes into account additional cooking methods and describes its method to combine estimates for various cooking methods into exposure point concentrations (as consumed) for the risk characterization. Some of the data and methodology used in this report might be helpful to the authors of the catfish assessment.

Response 32

Catfish-associated cooking effects data were used whenever such data were available. In the absence of such data, data from other types of fish were used as model inputs.

Comment 33

The range of cooking loss for nitrofurans is overstated based on the paper cited (Cooper & Kennedy 2007). The cooking loss data is based on pig muscle and liver. The data on pig muscle is most appropriate to use as the fat content is likely more closely that of catfish flesh. As expected, there is greater loss from cooking liver with its higher fat content.

Response 33

The revised risk assessment focuses on *Salmonella* effects.

Comment 34

Cd bioavailability/absorption from fish:

Based on my reading of the Cd absorption literature (c.f., ATSDR), the use of 13% bioavailability is several-fold too high. ATSDR estimated 3-6% absorption for individuals with adequate iron stores. At a minimum, this should be a distribution, perhaps triangular with a mean of 4-5%. However, it is not clear to me why cadmium is included as a hazard as it had a lower screening score than others, was present in 2% of the samples, and likely doesn't contribute to the risk.

Response 34

The revised risk assessment focuses only on *Salmonella* effects.

Comment 35

c. Are model outputs reasonable?

The points addressed previously lead to both overestimates and underestimates of the underlying risk, although I think it is more likely that the risks are underestimated than overestimated. In my opinion, the absolute risk values are unreliable including the number of adverse consequences avoided, although the relative risks (outcomes as percent differences between baseline and FSIS inspection) may be ok.

Response 35

FSIS acknowledges that there is uncertainty associated with the risk assessment's best estimates of adverse effects. This uncertainty has been addressed in the uncertainty analyses.

Comment 36

d. Is the evaluation of uncertainties sound?

The evaluation of uncertainty is extremely limited. In terms of parameter uncertainty, it focuses only on the single datasets selected for use, not all the data for the parameters available. It does not include any model uncertainty, including the uncertainty associated with the selection of the functional form with which to model the data. It does not deal with any of the toxicological uncertainty, and the limited amount of toxicity data incorporated. It does not deal in a serious way with interactive effects of these compounds although data are available in this regard.

Response 36

Given the limited data available for most hazards, it seems that uncertainty analysis beyond (i.e., more detailed than) that considered in the original report is unnecessary. We have established both very conservative and very non-conservative input values to the model and generated extreme predictions on either side of our default predictions. Model uncertainty (i.e., different choices for concentration distributions based on the same limited data) would generate much more limited ranges in our predictions relative to the results we obtained.

Comment 37

The uncertainty (bounding) analysis is based on the model inputs found to be most influential in the sensitivity analysis. Meal size is not included in this, nor does it appear to be part of the sensitivity analysis. This omission is surprising to me as meal size should be proportional to dose, and thus more influential than, say cooking loss (for chemical hazards).

Response 37

The inputs for size of individual meals were based on much better data than many other model inputs. The dose consumed is the product of initial contamination, serving size and any effects of growth/cooking. It was assumed that our uncertainty about the random variables for initial contamination and growth/cooking effect was greater than our uncertainty about the random variable for serving size.

The revised risk assessment focuses on *Salmonella*. Serving sizes were updated based on the most current data available and the output of the revised model. Sensitivity analysis with respect to size of serving in that revised assessment.

Comment 38

5. Comment on the risk assessment model. As a general matter, comment on the hazards identified in the assessment? Have we failed to identify important hazards? In addition:

a. Chemical Hazards

i. Are the methods utilized to identify the most significant potential hazards associated with consumption of catfish valid?

I am not familiar with the equations used for priority ranking score and the underlying rationale, and there is insufficient information presented to make any judgment about them. Perhaps these could be explained in more depth in an appendix. In general, the factors included seem appropriate. However, I don't understand the rationale for the selection of the high priority hazards based on the toxicity scores. Why is the high priority cutoff between 10 and 13 for the organic compounds (organophosphates in, diuron out) while it goes down to 4.6 (cadmium in) for the inorganic compounds?

Response 38

This approach was used to include a variety of potential chemical hazards in the risk assessment. If one class of compounds appeared to be associated with significant risk to catfish consumers, we would likely then evaluate other compounds with similar chemical properties and use patterns. However, the revised risk assessment focuses only on *Salmonella*, and the effects of chemical compounds are no longer considered.

Comment 39

i. Are the approaches utilized to estimate exposure and level of concern resulting from the consumption of catfish valid?

Exposure evaluation for acute effects: The only exposure outcome evaluated is the annual per serving exposures. Furthermore, there is no allowance for more than one catfish meal/day. This exposure evaluation cannot be used to calculate acute effects; those where the exposure period is a day to a week. I am sure there are cases where individuals consume more than one catfish meal in a 24 hour period or have more than one serving per meal. People eat leftovers or go to fish fries. These are the conditions under which to evaluate whether or not acute effects will occur.

There is a mistake on p. 44 in describing the conversions to match input for the dose response function: $mg/Kgbw)^{33}$ is not meaningful.

Response 39

Analysis of the 1996-2006 NHANES consumption data suggest that consumption of multiple catfish meals in a single day is rare.

The metric in question refers to mg of the hazard per kilogram bodyweight of the catfish consumers. However, the revised risk assessment focuses on the microbial hazard *Salmonella* where the bodyweight of consumers does not enter the calculations.

Comment 40

i. Are the approaches utilized to estimate the prevalence of adverse effects (acute and chronic) resulting from hazard exposure valid?

The selection of non-cancer hazard endpoints seems arbitrary. While it is reasonable to select various cardiovascular endpoints, the intense scrutiny of them and not many other adverse outcomes seems disproportionate. The chemicals included in the risk assessment are associated with many other hazards, including kidney disease, immune system dysfunction, and nervous system effects (other than IQ). PCBs and DDTs are endocrine disruptors associated with neurodevelopmental and reproductive effects; these effects can be observed at low doses associated with environmental (food consumption) exposure.

Response 40

As noted by the reviewer, the chemicals included in this risk assessment may be associated with a variety of adverse effects. As the purpose of this risk assessment is to estimate the magnitude of adverse effects associated with catfish consumption, we limited our estimates to chemicals and adverse effects for which dose vs. response functions were

available or could be derived. However, the revised risk assessment focuses on *Salmonella*, and the effects of chemical compounds are no longer considered.

Comment 41

There should be some discussion of why a Poisson (normal) distribution was used to model adverse effects. My experience with environmental variables and toxicity data is they are more likely to be log-normally distributed (hence the use of log-dose with the probit function when determining acute effects such as LD50).

Response 41

It is not clear what this comment refers to. If it is the choice of Poisson for modeling variability (randomness) of annual total illnesses, then our rationale is that we chose this distribution for simplicity. Such an assumption (that annual human illness counts are described by a Poisson distribution) is a reasonable default when it is not possible to empirically estimate variability. The model predicts an (average) annual rate of human illnesses. Because the Poisson has a variance equal to its mean, we can use our prediction of the model as the mean and variance of annual illnesses.

The lognormal variability referred to in this comment is more appropriate when describing the variability in exposures across servings. This variability is integrated through a dose-response function so that a single probability of illness (given exposure) results (*e.g.*, Equation 11 in the original risk assessment). In other words, the lognormal (or otherwise skewed) exposure distribution does not translate to the variability in total illnesses predicted.

Comment 42

a. Microbial Hazard

ii. Are the methods utilized to identify the most significant potential hazards associated with consumption of catfish valid?

Food safety/microbial hazards are not an area of expertise for me. I could not determine, from the information provided in the report and Appendix II, how the determination was made to include *Salmonella* in the risk assessment, but not the intermediate priority microorganisms such as Listeria monocytogeneses, C botulinum and the fecal bacteria. It seemed the criterion was an epidemiologically confirmed outbreak (for *Salmonella*). However, Listeria and others have been detected in catfish, including processed fillets and E. coli strikes me as a plausible and hazardous contaminant.

Response 42

We have addressed concerns about *Listeria monocytogenes* in our response to Comment 10. The same reasoning holds for C*. botulinum* and

fecal bacteria, which are also discussed in the paper cited in the response to comment 10.

Comment 43

i. Are the approaches utilized to estimate exposure and dose-response resulting from the consumption of catfish valid?

As stated earlier, I think the data used for serving size was too limited, and this is linearly related to *Salmonella* exposure. I am not familiar with the dose-response function, but it appears to be widely used and accepted.

Response 43

The 1996-2006 NHANES consumption data constitute the most complete catfish consumption data identified by the Agency.

Comment 44

i. Are the approaches utilized to estimate the prevalence of adverse effects (acute and chronic) resulting from hazard exposure valid?

The presentation of the health effects in the various scenarios is confusing – a small table summarizing the effects would help. I understand from the numbers about the reduction in hospitalizations with the FSIS inspection, but I cannot reproduce the estimates of deaths. There may be a calculation error or a typo regarding the predicted number of deaths.

Response 44

The revised risk assessment will only predict total salmonellosis cases (and cases avoided). Outcomes of cases will be addressed in a benefit-cost analysis.

6 REVIEWER NUMBER 3

Comment 45

1. Model documentation:

a. Is the report clearly written?

The report is generally superbly written, with one major exception, and some minor exceptions, as detailed below in (e). Particular strengths include very clear text and excellent use of tables.

b. Does it completely cover all aspects of the analysis?

Yes, with one major exception, as detailed below in (e).

c. Does it follow a logical structure and layout?

Yes, extremely so - my congratulations to the authors on this aspect.

d. Where data are included/excluded, does the documentation provide adequate justification?

Yes, documentation is generally appropriate with the exception of the description of the potential CVD effects of lead exposure (p. 49-50). First, the authors should clarify whether gender-specific RR's were utilized, as were presented in the Fewtrell report.

Second, and more importantly, the authors should specify that these RR's are based on largely cross-sectional observational associations between blood lead levels and blood pressure levels, and then secondary extrapolation of these blood pressure differences to prediction of future CVD endpoints. It should also be specified that a relationship between lead exposure and actual CVD endpoints has not yet been established in prospective studies.

Finally, the counterfactual must be clearly specified, both here and elsewhere (see (e) below): these estimates are not for the effect on CVD risk of current catfish consumption, including current lead contamination, compared to no consumption, but rather for the effect of current catfish consumption, including current lead contamination, compared with equivalent catfish consumption that is wholly lead-free. The reason for this specification should also be detailed: i.e., that because catfish consumption also provides beneficial nutrients, particularly omega-3 fatty acids, that will reduce CVD risk (and also lower blood pressure), these estimates should not be construed to be the effects of current catfish consumption per se, which is likely reducing overall CVD risk in the US, even given the current lead content, compared to no catfish consumption at all.

Response 45

While we can appreciate the points raised in this comment as pertinent to an analysis of consumer behavior and public policy with respect to encouraging/discouraging catfish consumption, the counterfactual benefits of catfish consumption were not relevant to our goal of estimating the public health benefits of a rule concerning catfish *inspection*.

Comment 46

e. Alternate outline and/or approach for documenting adequately and clearly this risk assessment.

The model is clearly written and presented, with one major, and extremely important, exception:

**Throughout the document, the authors state that the baseline model estimates the adverse health effects of current catfish consumption based on current contaminant levels, describing for example, the "human health impact due to catfish consumption" (p. 15), "health effects associated with respect to the consumption of contaminated catfish (p. 15), "probability of an adverse effect associated with the consumption of one catfish meal" (p. 19), "estimation of the mean probability of each adverse public health effect per catfish meal" (p. 20), "hazards due to catfish consumption" (Figure 2); "the annual rate of adverse effect r in the US population" (p. 52), "estimates of catfish-consumption-associated hypertensive disease" (p. 58), "catfish-consumption-associated adverse effects" (p. 59), results of Tables AIV.3, AIV.4, and AIV.7, etc., etc.

However, for two of the major outcomes assessed (IQ, CVD), the accuracy of the baseline and post-FSIS estimates are strongly dependent on the <u>choice of the counterfactual</u>, that is not clearly specified in the document. For both IQ and CVD, the models do not estimate the adverse health effects of current catfish consumption, based on current contaminant levels, <u>compared to no such consumption of catfish</u>. Rather, the models estimate the adverse health effects of current consumption of catfish, based on current contaminant levels, <u>compared to the same level of consumption of catfish containing zero contaminants</u>.

Response 46

Our response to Comment 45 partly addresses this comment. Since only the predicted number of annual salmonellosis cases prevented is used in the benefit-cost analysis, the revised catfish risk assessment focuses solely on the adverse public health outcome associated with the consumption of *Salmonella*-contaminated catfish.

Comment 47

These counterfactuals are very different. For the former, the model must consider the entire effect of the catfish meal, that would include the hazards but also the beneficial

nutrients in catfish. For the latter, only the hazards may be considered (given the assumption that the beneficial nutrients are unchanged by removal of the hazards). As this risk assessment considers only the hazards, clearly the latter counterfactual is the one appropriate to this document – this should be specified and discussed in detail.

Unfortunately, the authors do not specify the counterfactual, so the accuracy (and interpretation) of the estimates can be brought into question. Indeed, based on most of the language in the document in which the authors describe what they are estimating (e.g., examples above**), the document strongly implies that they are quantifying the former estimation (i.e., the effect of currently contaminated catfish consumption compared to no such consumption). Notably, this interpretation of the counterfactual would render both the IQ and CVD estimates markedly incorrect.

Catfish contain omega-3 fatty acids that will both improve IQ and reduce CVD risk. Thus, to estimate the true "human health impact due to catfish consumption", or "estimation of the mean probability of each adverse public health effect per catfish meal", or any of the other descriptors above, for both IQ and CVD outcomes, both the risks and the benefits must be considered <u>if</u> the counterfactual were the effect of a current catfish meal compared to no such consumption. To perform this estimation correctly, this would require modeling the benefits of the average omega-3 contents of catfish on both IQ and CVD risk, and then summing of the risks from contaminants and benefits from omega-3 fatty acids. Valid data, of much better quality than that used to model the risks, are available to perform such assessments of benefits. If this were done, it is highly likely that the overall estimated effects of current baseline catfish consumption, including current contaminant levels, on both IQ and CVD in the US will be beneficial, not harmful.

Of course, these absolute benefits of catfish consumption would increase even further if fewer contaminants were present in the catfish post-FSIS, in that the benefits of the omega-3 fatty acids on IQ and CVD would be even less offset by the harms of the contaminants. Thus, whereas the overall absolute estimates for IQ and CVD effects of both baseline and post-FSIS catfish consumption, compared to no consumption, would be different if benefits of omega-3 fatty acids were modeled appropriately, the net estimated change ("delta") comparing baseline vs. post-FSIS would not be different. This is because the overall consumption of omega-3 fatty acids should be the same in the baseline vs. post-FSIS models, so that the corrections to both models for the benefits would offset each other in the calculation of the difference.

Because the main intent of this document appears to be the estimation of the relative effect of the FSIS program, rather than of the absolute effects of current baseline or post-FSIS catfish consumption per se, it would be much simpler to retain the current estimates and simply specify the counterfactual explicitly throughout the document. That is, the appropriate description of both the baseline and post-FSIS models is the effect of catfish consumption on outcomes, compared <u>to the same level of consumption of wholly contaminant-free catfish</u>.

If this counterfactual were clearly specified throughout the document, each time any estimates of the "health effects" of a catfish meal were mentioned, then the document would be clear and correct. These issues should also be clearly described in the Introduction, discussing the benefits of omega-3 fatty acids on IQ and CVD and explaining why the baseline and post-FSIS assessment cannot be construed as estimates of the health effects of catfish consumption per se, but rather of the health effects of catfish consumption with baseline or post-FSIS contaminant levels compared to the same level of consumption of catfish with zero contaminants. The Introduction and Conclusions should also specify that the actual health effect on IQ and CVD of current catfish consumption per se, compared with no consumption, is likely beneficial, and that the post-FSIS model approximates how much more this benefit would increase.

For clarify, it can also be noted that for the *Salmonella* and cancer outcomes, the choice between these two counterfactuals (no consumption vs. equivalent consumption of wholly contaminant-free catfish) will not have a major effect on the baseline or post-FSIS estimates, as there is little evidence that omega-3 fatty acids (or other non-contaminant beneficial factors) in catfish have any appreciable benefits on risk of *Salmonella* or cancer.

Response 47

The estimates resulting from this risk assessment do not represent the total health effects associated with catfish consumption. The objective of this risk assessment is to estimate the impact of an FSIS inspection program on adverse effects resulting from the ingestion of hazards that are potentially associated with catfish. The risk assessment determines the change (increase) in adverse effects resulting from hazards that are co-ingested with catfish. These effects are relative to the level of these adverse effects that are experienced in a population which consumes catfish containing no residues of the hazard of interest, not to the population that consumes no catfish. The beneficial effects associated with the consumption of nutritious compounds in catfish contribute to the background levels for such effects. Adverse effects resulting from the ingestion of hazards are assumed to be independent of potentially beneficial substances that are natural constituents of catfish. The risk assessment assumes that implementation of an FSIS regulatory program will not impact the amount of catfish consumed in the US. Therefore, the background levels of these adverse effects and health effects are constant.

Comment 48

Other points for improving clarity:

Table 9: Impact of each scenario should also be shown per 100,000 persons per year, to clarify the size of the effects that are being considered here. This point is briefly made in the summary (p. 78), but this will be lost in the full report and many people will focus on the Tables alone. Alternatively, the percentages of estimated overall cancer, CVDs, and

total IQ points that these estimates represent could be added to the Table (see comment related to page 59, below).

Response 48

This approach will add clarity and will be included in future reports as appropriate.

Comment 49

Page 57: The statement that it "appears extremely unlikely that catfish-consumption-associated prenatal mercury exposure would result in an intelligence-deficit-associated disease (e.g. mild mental retardation)" is still far too generous to the potential for any such effects. It would be more appropriate to state that "On an individual basis, the likelihood that catfish-consumption-associated prenatal mercury exposure would result in an intelligence-deficit-associated disease (e.g. mild mental retardation) is negligible or virtually zero. This is even more likely the case if the likely benefits on IQ from catfish-consumption-associated prenatal omega-3 fatty acid exposure, that were not considered herein, were to be taken into account." Similar corrections are needed for the statement on catfish-consumption-associated prenatal lead exposure: "On an individual basis, the likelihood that catfish-consumption-associated prenatal lead exposure would result in any measurable decrease in an individual's intelligence or an intelligence-deficit-associated disease (e.g. mild mental retardation) is negligible or virtually zero. This is even more likely the case if the likely benefits on IQ from catfish-consumption-associated prenatal omega-3 fatty acid exposure, that were not considered herein, were to be taken into account."

Response 49

The effects of chemical hazards are not considered in the revised risk assessment.

In developing this risk assessment, we estimated the public health impact as the difference between the current regulatory situation and an FSIS style program. It is likely that the beneficial effects of catfish consumption referred to by the reviewer would be constant under both scenarios. As such, these beneficial aspects will not affect the public health impacts associated with the risk assessment.

Comment 50

Page 59: The reporting of the percentage of estimated overall cancer in the U.S. reflected by these estimates is a very good use of data to present the findings clearly. Similar numbers (i.e., percentage of overall incidences) should be included at the end of the previous section for the estimates of hypertensive, cerebrovascular, ischemic heart, and other cardiac diseases. All this data (i.e., for both cancers and CVDs) should also be added to Table 9, e.g., in a new column or as a footnote.

Response 50

This approach will add clarity and will be included in future reports as appropriate.

Comment 51
2. Validity of the model:
A. Input distribution for each hazard in the analysis
a. Are these assumptions logical and adequately justified?

It seems a reasonable (although unproven) assumption that the FSIS impact on *Salmonella* prevalence in catfish will be similar to the historical FSIS impact on *Salmonella* prevalence in beef and poultry (page 22).

However, the assumption that the FSIS impact on each of the other hazards in catfish will be proportional to this same metric (the historical FSIS impact on *Salmonella* prevalence in beef and poultry) (page 22) is bizarre, without any presented justifications for this seemingly radical assumption. What evidence exists that the impact of FSIS regulation on any of the other contaminants will be even remotely similar to this metric? I cannot think of any. A wide range of diverse processes influence levels of DDT, PCBs, organophosphates, lead, and mercury in foods. PCB levels, for example, are decreasing steadily over time in all foods - what evidence is there that the FSIS program would have any meaningful impact on this slope of decline? Similarly, what evidence is there to support the assumption of proportional (to the stated metric above) declines in lead or mercury levels post-FSIS? This assumption seems to be a dramatic stretch, with major implications for the results, and must be justified with appropriate evidence or altered.

Response 51

We lack empiric evidence about the effectiveness of a proposed program for catfish, and must make our case by analogy. If our assumption about program effectiveness was optimistic, then our predictions about adverse outcomes avoided by the program were also optimistic. We think this comment supports our decision to focus the revised risk assessment on *Salmonella*. This revised risk assessment only references FSIS experience with reducing Salmonella occurrences among poultry.

Comment 52
b. Is the selection of data appropriate?

Yes.

c. Are model outputs reasonable?

Yes.

d. Is the evaluation of uncertainties sound?

Generally yes, and the sensitivity analyses are generally excellent and a major strength of this report. Two important revisions are needed:

1. The dose-response functions are the most uncertain input for most of the compounds, particularly for each of the compounds that already include uncertainty factors in their estimation of effects. Based on this, an increase in slope of 50% is reasonable, but a decrease in slope of only 50% is far too small. The slopes of each response should be shifted downward by at least as much as the average uncertainty factor (likely several fold) used in their estimation.

2. Sensitivity to changes in the impact of the FSIS regulation (e.g., ranging from 25% to double that of the historical effect on *Salmonella* in beef/poultry) should be added.

Response 52

The sensitivity analysis is intended to highlight the model inputs that are most influential on the model's output. The elasticity measure is a convenient technique for examining sensitivity. Nevertheless, this approach to sensitivity analysis may be limited because it only examines local effects (i.e., effects based on small changes to the inputs) rather than global effects that measure the influence of large changes to the inputs. This comment seems more relevant to a scenario analysis in which (multiple) model inputs are adjusted to plausible alternative values and the effect on the model output is noted.

We appreciate the need for additional analysis of the sensitivity of our predictions to different assumptions about the effectiveness of FSIS inspection. The revised risk assessment examines the effectiveness of FSIS inspection in greater detail than was presented in the original risk assessment report.

Comment 53

B. Distribution of catfish consumption frequency and amount of catfish consumed in each age-sex category.

a. Are these assumptions logical and adequately justified?

Generally, yes. Two errors are noted. First, whereas 24-hour recall data provide unbiased estimates of true population (or subgroup) mean consumption levels, the population (or subgroup) distributions of consumption are overestimated due to within-person error, reflected for example in broader variances, SDs, or percentiles. Thus, the variances and distribution percentiles of consumption (page 40) should be corrected for this well-known error. This can be accomplished directly in NHANES by evaluating the data from the more recent cycles that contain two 24-hr recalls per person. Using this data, the within-person vs. between-person variance in consumption can be determined; only the latter should contribute to the population (or subgroup) variances.

For similar reasons, the statement that the NHANES data "likely represents regular catfish consumers and not occasional consumers" (page 41) is incorrect. Each 30-day response period is a random sample of each individual's consumption over the year (ignoring seasonal effects, that are difficult to capture and control in NHANES and thus can be assume to be random), and thus provides an unbiased estimate of the mean U.S. population consumption over 30 days, that therefore includes both regular and occasional consumers. As above, the SD or variance of this mean consumption will be overestimated, but the mean is unbiased and includes all (regular and occasional) consumers. The discrepancy with the production data (page 41) is therefore due to other reasons, such as waste, other inaccuracies with the NHANES data, inaccuracies with the production data, etc.

Page 41, last sentence: "The estimated number of U.S. catfish meals consumed per year was used for calculating…" Based on the previous sentences, "The estimated number" to which this statement refers is unclear. Does this refer to the estimated number from NHANES data, or the estimated number from production data? It should be (and I assume it is) the former, but this should be clarified here.

Response 53

The estimated number of U.S. catfish meals consumed per year was calculated from the 1996-2006 NHANES data variable recording the responses of 2,979 subjects that reported the number of times catfish was consumed over a 30-day period.

Comment 54

b. Is the selection of data appropriate?

Yes.

c. Are model outputs reasonable?

Yes, except as noted above.

d. Is the evaluation of uncertainties sound?

Yes.

3.Risk assessment model.

General comments on the hazards identified in the assessment. Have the authors failed to identify important hazards?

All appropriate relevant hazards are identified, and the methods are sound, objective, and clearly described.

a. Chemical hazards

i. Are the methods utilized to identify the most significant potential hazards associated with consumption of catfish valid?

Yes.

ii. Are the approaches utilized to estimate exposure and level of concern resulting from the consumption of catfish valid?

Generally yes. Strengths are broad use of published findings to estimate contaminant levels; methods to adjust for storage, preparation, and cooking; separate estimates for

domestic vs. imported catfish; standardization to age and gender of consumers; and use of NHANES to provide nationally representative estimates of mean levels of consumption.

Distributions of catfish consumption require correction for within-person vs. between-person variance, as described above.

The methods used and their assumptions (and the counterfactual) should be specified for estimated effects of lead on CVD, as described above (see 1.d.)

iii. Are the approaches utilized to estimate the prevalence of adverse effects (acute and chronic) resulting from hazard exposure valid?

Generally yes.

The use of uncertainty factors requires further discussion and consideration. It must be clarified, for example, that all the estimates that utilize uncertainty factors (page 45-46) represent the upper bound of actual risk, and that the true risk may be considerably smaller. For example, interspecies variation could also result in lower risk in humans compared with animal studies, but we never use uncertainty factors <1.0 to account for this. Moreover, whereas use of uncertainty factors to account for interspecies variation is reasonable (so that the estimates represent the upper bound of actual risk), the use of uncertainty factors to account for intraspecies (human to human) variability is <u>not</u> valid for the estimation of total population effects. Accounting for intraspecies variation is reasonable when the goal is to define a tolerable level of exposure to protect sensitive subgroups in the population. However, when the aim is to estimate total population effects (as in this analysis), only the average overall effect on the population is relevant, that implicitly already includes some persons at higher and others at lower vulnerability. Thus, when estimating population effects, use of uncertainty factors to account for intraspecies variation "stacks the deck": the overall population effects are incorrectly estimated by basing the population hazard on the hazard in the most sensitive subgroups, which is clearly invalid. The range and values of the uncertainty factors should be correspondingly reduced to remove for any accounting for intraspecies variation.

Response 54

> The use of intraspecies uncertainty factor is consistent with the widely held assumption that human-to-human responses are more variable than the rodent-to-rodent responses observed in homogenous laboratory animals.

Comment 55

Clarification is also needed for the following:

1. Are the cumulative probabilities truly "summed" across all relevant hazards? Probabilities should not be summed but multiplied. For example, two hazards that each increase the probability of an adverse outcome by 5% will together increase the

probability by 9.75% (1 - 0.95*0.95), not 10%. These differences will not be major for low probabilities, but there is no reason not to compute the total effects correctly.

Response 55

It is unclear to what the commenter is referring, but, it may represent confusion between the intersection and union of two events. We are not determining the probability of acquiring disease X and disease Y (which is an intersection of probabilities and calculated as described in this comment). We are determining the probability of acquiring disease X or disease Y in a total probability sense. This latter probability is a union of two events and reflects the sum of the two probabilities (minus any overlap in occurrence of diseases X and Y together – which we assume to be zero given the generally low probabilities).

Comment 56

2. For the estimates of mercury and lead effects on IQ that "were based on the estimated yearly consumption of catfish" (page 47), what estimated yearly consumption of catfish was used: estimates from the whole U.S. population, or only from women of child-bearing age? The latter should be used and specified.

Response 56

For this purpose the risk assessment used only women of child-bearing age.

Comment 57

3. Table 9: Why is the IQ impact of [S]iluriformes consumption more than 10-fold higher than the IQ impact of [I]ctaluridae consumption, when the corresponding comparative impact of [S]iluriformes vs. [I]ctaluridae consumption is only approximately 2-fold for every other outcome? This could only be the case if average mercury levels in [S]iluriformes were far higher (approximately 5-fold) than in [I]ctaluridae - is this the case? If not, why do these estimates differ so dramatically?

Response 57

The revised risk assessment focuses on *Salmonella*, and the effects of chemical compounds are no longer considered.

Comment 58

Of note, a clear strength of the analysis is the lack of estimation of CVD effects attributable to mercury. While this topic is hyped in the media, the present data for CVD effects of mercury are limited and highly contradictory, and the authors appropriately have not included these presently unestablished effects in their models.

b. Microbial hazard

i. Are the methods utilized to identify the most significant potential hazards associated with consumption of catfish valid?

Yes.

ii. Are the approaches utilized to estimate exposure and dose-response resulting from the consumption of catfish valid?

Yes, well-done using standard and accepted methods.

iii. Are the approaches utilized to estimate the prevalence of adverse effects (acute and chronic) resulting from hazard exposure valid?

Yes.

Response 58

No response needed.

7 REVIEWER NUMBER 4

Comment 59

A. Is the report clearly written?

Some aspects are quite clear. There is clarity in the description of the issue; the regulatory framework; the interpretation of results.

The description of the methodology, however, is not at all clear – or at least is not clear to someone trying to reproduce the results. I realize you can't have too much mathematical detail in the report (this could be placed into an appendix), but where the report really fails is in conveying the calculational steps and the ways in which these are related to the particular issues of probability I mention below.

Response 59

The revised risk assessment focuses on *Salmonella* and describes more fully the mathematics of the model.

Comment 60

I comment first on the Executive Summary. This section is quite well written in regards to ease of understanding. The most important results are included, although they are almost impossible to interpret as to public health significance because the size of the consuming population is not given. For example, a decrease of 1670 points in IQ would be alarming for a population of 100 people, but of no real consequence if spread uniformly across a population of a million people (and Table 6 later suggests it is in the millions). The way around this problem is to take the approach the USEPA used in their most recent assessment of the risks from Pb in air (i.e. the Pb NAAQS Risk and Exposure Assessment, 2008). They estimated the number of people with an IQ loss at different levels (1 point, 2 points….10 points, etc). They established a level of IQ loss they felt to be clinically significant (that level may differ between the two organizations), and only then reported the probability of, and number of people with, an IQ decrement larger than the threshold level.

The Executive Summary should also at least briefly specify the inspection program considered. What are the catfish being inspected FOR (i.e. what is being measured)? Is the proposal (given later in the report, but not here in the Executive Summary) examining the fish for each of the compounds for which risks are calculated; or some subset? At what point in the food production chain will the inspections occur? What evidence is there that the inspections will result in the kinds of detection rates needed to significantly reduce the risks? Again, some of these questions are addressed later in the document, but they are important enough to at least mention in the Executive Summary. All inspection programs have failures, and the rate of failure of the system must be characterized and included in the risk assessment, even if the data and past experience simply indicate that inspection programs are sufficiently reliable to consider the failure of the program (to catch significant cases of contamination of the fish) to be so unlikely as to not affect the risk estimates. I doubt, however, that this is the case.

Response 60

The revised risk assessment includes an expansive qualitative description of how the model considers the effectiveness of FSIS inspection. Additional characterization of uncertainty about this effect was included in the updated risk assessment.

Comment 61

Page 15 provides the only hint as to why this program of inspection is being considered. A reader may be wondering why the program is required – what is it in past experience that causes catfish in particular to be of regulatory concern? This paragraph, however, doesn't explain the situation very well; it should be improved. It mentions that there were contaminants "in and/or around catfish farms". The latter half, "around catfish farms" doesn't seem to me very compelling. What matters is whether the catfish come into contact with the contaminant, and what the bioaccumulation factor is. This information is never specified. To the authors' credit, the issue is clarified later to some extent by making it clear that the prioritization process looked only at the level of contaminant in tissue.

Response 61

The issue of bioaccumulation is no longer relevant since the updated quantitative risk assessment focuses *Salmonella* contamination.

Comment 62

Nor is the claim that there were "7 possible catfish-associated outbreaks" compelling. Outbreaks of what? I presume some sort of microbial disorder, but as a reader I am not provided the information to determine this. Still, the approach of establishing priorities, using the methodology described later, to narrow a large potential list down to 11 is a good one and follows the practice of the field.

Response 62

For *Salmonella*, the number of human outbreaks potentially involving catfish is one, which occurred in 1991. This outbreak is now explicitly considered in an analysis that attempts to validate the model's prediction of annual cases of salmonellosis. This one outbreak is used in the context of all foodborne outbreaks (where food vehicles were identified) to determine the fraction of illnesses attributable to catfish.

Comment 63

On page 16, the reason for considering Siluriformes rather than solely Ictaluridae is provided. I can understand the reasoning here, but was also wondering whether it is either (1) not possible to separate Ictaluridae from others in the Siluriformes category at the market, and inspect only the former, and/or (2) likely that if Ictaluridae poses a risk, so do the other members of Siluriformes. If either of these holds, the case for monitoring all Siluriformes seems good, but it would be a waste of resources to examine all of the

members simply because some parts of the market incorrectly label some fish as catfish. I imagine that there may be some reason why catfish are of particular interest (such as having high fat content that can bioaccumulate contaminants), and so one wants an inspection program that focuses on fish with this same characteristic, not just fish that happen to also fall into Siluriformes or Ictaluridae.

Response 63

USDA has yet to determine the definition of catfish: this decision is pending and is beyond the scope of the risk assessment.

Comment 64

B. Does it completely cover all aspects of the analyses?

All aspects are at least mentioned, but it is very difficult, as I say above, to understand the sampling process being used. I will try here to explain where the confusion lies. I will assume one wants to know the number of occurrences of a disease in the population due to catfish consumption. From Table 6, I would assume there some 2.5 billion servings in a year. I could imagine a process in which I sample a concentration at random (from different distributions depending on whether this is a pre or post FSIS program, and depending on whether the serving is assumed to be imported or domestic). Then I would multiply by sample size to get total intake (from an age distribution). Then I would divide by body mass (from an age-sex category's distribution). Then I would use these results to calculate an ADRI for that particular event. Then I would calculate a hazard quotient. I would repeat this process many times, and keep track of both how many events I had modeled. I would then determine the number of these events that had an HQ above 1 and divide this by the total number of events to get the fraction of events producing an effect (for a non-cancer effect here). This fraction would be multiplied by the 2.5 billion servings or events to get the total number of adverse effects. Some variant of this is what underlies the calculations in the report. For cancer and IQ loss, one uses the dose-response function rather than an HQ calculation, but the approach is otherwise the same. This is what I expected to find in the report, but I was left wondering what approach really was used, because the authors never give a clear description of the sampling process or the population to which it is being applied.

Response 64

We attempted to estimate the magnitude of adverse effects in the population of U.S. catfish consumers. The approach outlined (i.e., the "hazard quotient" approach) does not permit the estimation of the magnitude of the adverse effects.

Comment 65

C. Does it follow a logical structure and layout?

Yes, it is logical by way or organization of material, but not by way of describing the process of reasoning through the steps of calculation. This aspect of the paper needs to be greatly improved, with an ideal improvement being a flow diagram for the Monte Carlo approach.

Response 65

A flow diagram has been included in the revision (See Figure 1 of report).

Comment 66

Section 2.5 describes the overall model structure. It has a problem in that it immediately approaches the issue of the Monte Carlo methodology and the calculation of probabilities (or more properly, frequencies, as the analysis performed is not an uncertainty analysis but rather an inter-subject variability analysis – a distinction the authors need to make clear). My primary concern is that the section doesn't explain how the models are structured. What the assessment did was to (1) develop a set of models based on mean behavior, exposure and dose-response; (2) to develop inter-subject variability distributions for key parameters in these models; (3) propagate this variability through the suite of models using the Monte Carlo method; and (4) generate probability density functions from the output. Before the reader is told anything about the Monte Carlo aspect, they should be told the nature of the "mean value" model, as this is the core model that will be wrapped inside the Monte Carlo methodology.

Response 66

This comment seems to imply that a "mean" value can be propagated through a model that includes a non-linear dose-response. For *Salmonella*, this approach will not work because the mean risk of illness is not equal to the risk of the mean dose. For chemical hazards with a dose-response that is strictly linear in dose, a mean value prediction could be generated. Butthe revised risk assessment only pertains to *Salmonella*, so a "mean" value approach will not work. Nevertheless, we provide a detailed description of the solution algorithm in the revised risk assessment report.

Comment 67

The last paragraph on Page 20 is very confusing. It is not at all clear, from this one paragraph, how the assessors have modeled exposure. No information is given about the size of the population for which the various numbers apply. "Less than two" catfish meals are consumed per day, but by whom? Is this the average for the entire US population, or just the 19 million or so consumers of catfish? But then a later sentence mentions that mean probability was multiplied by the number of catfish consumers per year. If this is not the entire population of the U.S., there seems to me a disjoint between the calculation of average number of meals per person (presumably across the entire US population, although perhaps the authors mean across just the consumers) and the size of the population ultimately used to calculate incidence. And am I to assume that the entire consumption in a month, which the assessors state will be in the form of only one or two meals in the month, is spread uniformly (for purposes of calculation) across all of the days of a month? If so, that is fine, as it is standard risk assessment practice in calculating Average Daily Rate of Intake (ADRI) to use in a hazard quotient. But then much of the document reads as if the total intake from a given dining event counts as just one "event"

and is not spread over a period of time to get an ADRI value (remembering that ADRI is an average value over a long period of time, not an instantaneous one for a given day). The calculation is not well described so the reader can't be sure (the reader should not have to go back into the code to figure out this crucial element of the assessment model). Overall, this is a particularly poorly developed part of the report and requires improvement.

Response 67

The effects estimated in the risk assessment are limited to the catfish consuming portion of the US population.

We understand the reviewer's confusion. The task of generically explaining a risk assessment that considers both chemical and microbial hazards is daunting because the approaches can be very different. The revised risk assessment focuses on *Salmonella*, so the explanation of modeling is more specific. Modeling microbial hazards is focused on acute exposures, so these models determine the per-serving risk of illness. Furthermore, dose-response relationships for microbial hazards are not dependent on body weight, blood volumes/concentrations or other physiologic metrics.

Comment 68

In Section 2.5.1, I cannot be sure how the inspection program operates – in ways that influence the probability of a contaminated catfish reaching the table. The ratio of positive to negative detects is good information, but if the inspection program finds a contaminated fish, some number of other fish will need to be culled. The reader isn't told how this is done. Is the entire "catch" from which that contaminated fish was taken culled? Is it all catfish from that water body? If it is a Siluriformes but not an Ictaluridae, are all the Siluriformes members from that same catch or water body culled? It would be nice to provide this information and explain how this approach relates to the ways in which beef and poultry are culled (which is where the pre-and-post ratio of concentrations are obtained).

Response 68

The details of the proposed catfish inspection system are beyond the scope of the risk assessment.

Comment 69

And while I understand that the only ratio that could be developed was for beef and poultry, I see no reason to believe this same ratio will apply to *Salmonella* contamination in catfish. If the ratio were shown to be the same for beef as for poultry, that might make me a bit more comfortable, since it would show that the ratio is roughly similar for two very different species (and hence might also be similar for a third species – catfish). Or an argument could be made that the PROCEDURE is the same, and hence should be expected to yield similar results. I have a harder time accepting that, as the procedure surely has a lower limit of detection, and the levels of contamination in fish will be quite different from those in beef or poultry. And the culling procedures might differ. More of an explanation needs to be given here.

Response 69

The revised risk assessment includes an expansive qualitative description of how the model considers the effectiveness of FSIS inspection. In general, FSIS believes the effectiveness of its catfish inspection program will be similar to what its experience with poultry. Furthermore, the emphasis on sanitation in FSIS inspection programs will continue for catfish. The revised risk assessment explicitly recognizes the uncertainty we have about the effectiveness of an FSIS inspection program for catfish. There are two sources of uncertainty considered; the peak level of effectiveness achieved and the rate at which that effectiveness is achieved. Multiple possibilities for both these factors are considered.

Comment 70

In this same section, I am not sure how the modeling treats the other contaminants. For *Salmonella*, the assumption is that the mean concentration with the program in place is the ratio of concentrations in beef and poultry after and before an inspection program was put in place. But this does not mean the other 10 contaminants will be similarly affected. That depends entirely on how much correlation there is between these contaminants and *Salmonella*. I would guess there is little, and note also that *Salmonella* contamination is given by an index I later in Equation 3 (I will return to that in a moment). But the point here is that if the other contaminants are assumed to be reduced by the same degree as the *Salmonella*, there must be evidence of full correlation; and if they are not reduced at all, there must be evidence of a full lack of correlation. Neither assumption is mentioned or explained.

Response 70

The revised risk assessment focuses on *Salmonella* and the effects of the other 10 contaminants are no longer considered.

Comment 71

Equation 3 is somewhat confusing. X is the concentration of the contaminant at the point of production. It is not stated that this concentration is only for contaminated fish, and so I must assume it applies to ALL fish at the point of production. But then Equation 3 has the index I(h,y) which is 1 only if the fish is contaminated. Surely, the original point of production had a mixture of fish, some contaminated and some not, and so the fraction contaminated is hidden inside X. I don't, therefore, understand why I(h,y) is in Equation 3, unless it is being used as a variable that allows for the eventual effect of the inspection program, which presumably lowers the value of I(h,y) to some degree. The inspection program, however, could also be reflected in X if desired. This section needs to be written more clearly, as the reader will be particularly interested in how the inspection program's effects appear in the Equation.

Response 71

The revised risk assessment focuses on *Salmonella* and the effects of other contaminants are no longer considered.

Comment 72
The description to Equation 4 causes me to return to an issue I raised earlier: how several intakes, or catfish meals, in a month are treated. From the earlier report sections, I was assuming the assessors had taken total monthly intake and spread it uniformly across the days of the month to obtain an ADRI value for use in an HQ calculation. From the paragraph under Equation 4, however, the situation seems quite different. If indeed "servings" or "events" are being considered, that sounds as if an individual serving might contain the full intake from that serving rather than having that intake spread over a month to calculate an ADRI. By this point in the document, I was becoming increasingly confused as to how the calculations were being performed.
For example, consider a person who eats catfish twice a month, with a concentration of 1 gram of contaminant per kilogram of fish, and 1 kilogram of fish per serving. Under the ASDRI approach, the daily intake would be 2 x 1 x 1 / 30 (with the 30 being days per month). This is the value that would be used in the HQ calculation, and it would apply ON AVERAGE to all 30 days. In the "servings" approach, the person would have two servings in a month, each at 1 x 1. This value (of 1 x 1) would be used in the HQ calculation. Equation 4 appears to imply that the latter approach is being used. I can support such an approach (it is in my mind the better approach), but the writing in the report is not clear and so I can't be sure that is what is happening.

Response 72
The revised risk assessment focuses on *Salmonella* and the effects of the other 10 contaminants are no longer considered.

Comment 73
In Section 4.1, I generally support the methodology used. The authors have done a good job of explaining where they obtained the data; which distributions they chose to apply; and the characteristics of those distributions. I would simply ask that a sentence be added to each row of Tables 1 to 3 explaining WHY each particular distributional form was selected. This often is done by reference to a goodness-of fit criterion. In addition, an important feature of such distributions is often their truncation at high and low values. They tend to fit towards the middle of the data but not at the extremes. Perhaps I missed it, but I don't see that discussed here. This can be quite a significant issue when the risks are high only in the extreme tails.

Response 73
Our response to Comment 16 is applicable to this comment.

Comment 74
On page 40, the authors report a process that results in the same number of individuals in each age-sex category. This would usually worry me, because there is an age distribution in the US that is not at all flat. I am assuming, however, that this description really just means that the same number of individuals are sampled within each age-sex category,

and that the results are kept separate for each age-sex category. If later the sampling includes a randomly sampling of age-sex characteristics from the overall population, it would NOT be correct to have the same number of individuals in each age-sex category. The probability of an individual of a given age-sex being selected should be proportional to the fraction of the US population in that category (or if only consumers are considered, the fraction of consumers in that age-sex category).

Response 74

Age-sex categories were developed so that each group contained approximately the same number of respondents.

Comment 75

Equation 11 is not described clearly. The natural question to ask is what is meant by a "probability" here? Is it the probability that a randomly sampled individual will have exhibited one or more of the effects during a lifetime of consumption (I believe the answer is no)? Is it the probability that one randomly sampled exposure event (with a given age, sex, concentration, etc) will result in an adverse effect? I presume the answer lies in Equation 13, where these probabilities are multiplied by number of servings to obtain annual occurrences of effect per year. This suggests the authors are calculating probability of effect per consumption event (and further, given an earlier comment of mine, that they are NOT averaging intake over the days of a month, but rather calculating actual intake on a day when catfish are consumed). The authors need to state clearly what the probability is referring to so the reader can properly interpret the results. And I find it odd that for non-continuous effects, there is no description in the text as to how hazard quotients were developed and interpreted. This aspect of the report needs additional work.

Response 75

Equations 11-13 are necessarily generic for the risk assessment. For acute or non-cumulative effects (e.g., salmonellosis), the probability of illness is the calculated mean across all servings. For cumulative effects, the calculation was somewhat more complicated. We understand the reviewer's request for greater detail of the calculation in the report. Nevertheless, the revised risk assessment focuses on *Salmonella* and the calculations in Equations 11-13 accurately reflect the approach used for this hazard.

Comment 76

On Page 56, we come back to a problem throughout the document: defining the population. The authors state on this page that the IQ loss is spread across the "entire US population". I had been assuming, however, that the Monte Carlo sampling was being performed across only people who consumed catfish (some 19 million people). The calculations can be done either way and the number of effects will be the same (since if the entire US population is used, most of the random samplings of individuals will have no catfish consumption); the authors just need to be clear which is which.

On Page 57, the authors address a concern I raised earlier: that a 1700 or so point IQ loss is not large for several million people. They state, correctly, that it is unlikely any clinically important effects of IQ loss will be experienced from catfish consumption. This statement is not reflected in the Executive Summary, but should be.

Response 76

Indeed it would be more appropriate to have said " "across the entire population of U.S. catfish consumers;" However, this change was not included in the revised report which focuses on salmonellosis associated with the consumption of catfish.

Comment 77

D. Where data are included/excluded, does the documentation provide adequate justification? Yes, the authors have done a good job of describing the data. Section 3.1 does a good job of explaining the initial identification process for potential contaminants. I see no need for improvement here.

Sections 3.2 and 3.3 also are good explanations of the prioritization process. While this is always a contentious issue in hazard identification, the methods used here are as good as any others, and consistent with past practice at the organization, and so I support them here. In addition, the results obtained are reasonable based on my own past experience with fish (not catfish in particular, but rather fish more generally).

On Page 42, mention is made of breading causing a "20 to30%" decrease in the size of the catfish meal. This is too wide of a range. Did the authors use a Monte Carlo sampling between these extremes, and that is why a range is given? Or was a single value used throughout (and if so, which value was it – 20 or 30%, or a mean of 25%, or some other)?

Response 77

Monte Carlo sampling was used to sample between the extremes. The amount of breading was sampled from a uniform distribution ranging from 20 to 30%. This range of breading was derived from the Southern Region Aquaculture Center publication No. 185, "Processed Catfish" (November 1989).

Comment 78

On page 42, a method is mentioned for assigning imported vs. domestic concentrations. I assume the authors mean that the concentration selected was from a two-step process: (1) whether it is a domestic or imported fish is determined through a random number generator based on the fraction of fish that fall into each of the two categories and (2) once the category is determined, there is a random sampling of concentrations from within that category. This aspect of the study isn't explained well here and simply needs clarification (the computer code executed the step properly).

Response 78

The reviewer's assumptions are correct: the concentration selected was from a two-step process: (1) whether it is a domestic or imported fish is determined via Monte Carlo sampling from a binomial distribution based on the fraction of fish that fall into each of the two categories, and (2) once the category is determined, there is a Monte Carlo selection from the hazard concentration distribution for each hazard.

In addition, the revised model is written in a programming language that should afford interested reviewers the opportunity to directly review the coding and processing flow of the model.

Comment 79

Equation 6 concerns me for two reasons. First, the assessment has a combination of cancer and non-cancer effects. The former are usually estimated by probabilities, but the latter as hazard quotients. One can't sum them in any meaningful way (and so I doubt this is what the authors meant to convey). Second, summing hazard quotients to obtain what is in essence a hazard index requires the contaminants have a common or shared mode of action, or at least act on the same organ/tissue. That is not the case here. So, I am not sure what is meant by Equation 6, unless it is to be applied only to each specific category of effect (such as IQ loss, or to cancer), rather than across categories of effect. I could support the former, but not the latter. The report needs to clarify this issue.

Response 79

We agree that more clarity could have been provided. However, these equations do not appear in the revised risk assessment, which focuses on *Salmonella* only.

Comment 80

I agree with the approach in Equation 7, although the risk summary must eventually consider the case of an individual consuming catfish multiple times each year (22 times on average if Table 6 is to be used). But the results in the report suggest this was applied correctly.

D. Are the assumptions logical and adequately justified?

Once one can find the assumptions in the document, they do appear to be adequately justified. As mentioned above, however, it is quite hard to follow the logic used in the calculations, and so it also is hard to determine whether they are completely appropriate to the tasks. When I was able to determine this, however, the assumptions were appropriate. Where I could not perform this check is in the assumptions on the Monte Carlo sampling, since I could not find a clear explication of this procedure in the text.

Response 80

The updated risk assessment provides greater detail regarding the model solution algorithm presented below.

Mathematically, the average exposure dose of Salmonella[2] consumed in a random contaminated catfish serving is modeled as;

Equation 2 $D = X \times S \times G \times C$

where D *is one instance of an average exposure dose of Salmonella consumed,* X *is one instance of an average Salmonella concentration per gram of a contaminated catfish carcass,* S *is one instance of a catfish serving size (in grams consumed),* G *is one instance of the growth of Salmonella on a catfish carcass (to account for handling and storage between processing and consumption), and* C *is one instance of the expected reduction of Salmonella in a serving catfish caused by the effects of cooking. The inputs to this calculation (* X, S, G, C *) are random variables. The inputs for catfish serving size and the effect of cooking, however, are somewhat complicated.*

The risk assessment model uses Monte Carlo techniques to convolve the random variables (X, S, G, C *) that predict exposures for each of the four exposure classes and complete the numeric integration step described in Equation 3. The model is currently developed in the R software package (http://www.r-project.org/ Version 2.9.1), but is equivalently solvable in any software that supports Monte Carlo simulation. Each simulation of the model comprises three million iterations. Each model iteration represents a different contaminated serving of catfish across all four exposure pathways.*

Comment 81

E. Is the selection of data appropriate?

Yes, I am comfortable with this aspect of the analysis, including how data were assigned distributions for the sampling process. This comment applies to the data on concentration; ingestion amount; body mass; and the various health effects coefficients and benchmarks.

The treatment of IQ loss in Section 5.3 is fine, and agrees largely with a similar analysis performed by the EPA in looking at the NAAQS (National Ambient Air Quality Standard) for Pb. And the authors are correct in noting that this is a continuous variable.

The treatment of heart-related disease is also the same as in the larger EPA analysis, and is acceptable.

Equation 10 is a reasonable approximation of the dose-response characteristics of *Salmonella*, and so I have confidence in the data employed to develop this equation.

[2] Average dose of *Salmonella* is modeled because the beta-Poisson dose-response relationship is based on an average number of organisms in a serving. For example, if a value for average *Salmonella* dose of 0.2 CFU is used in the beta-Poisson, the function determines the probability that a serving will contain one or more CFU's (based on Poisson probabilities), as well as the probability that each integer unit *Salmonella* dose will result in illness (based on beta probabilities). Ignoring this aspect may lead to incorrectly including a Poisson function to determine integer *Salmonella* doses consumed in the exposure assessment; this would essentially 'double-count' the Poisson effect once the beta-Poisson relationship was included.

F. Are model outputs reasonable?

This is a strange question, because the "reasonableness" is not to be found in outputs but rather in the process producing these outputs. In general, there was nothing about most of the outputs that drew my eye to them and made me think the results were so far out of line with prior expectations as to be unreasonable (if that is what the question means). The one exception is the upper bound estimates of risk, which I find so far out of line with actual incidence of disease that I call into question whether that result is reasonable (with the error probably lying in the comments I made in Section 1 on this issue).

Response 81

We agree that the upper bounds of our uncertainty analysis are 'unreasonable'; these are reported as extreme predictions that represent the model's predictions when multiple inputs are simultaneously set at their extreme values. As we explain, we expect the "true" values for cases avoided to lie somewhere in between our extreme predictions.

A major driver for the range of illnesses avoided is the effectiveness of FSIS inspection. The revised risk assessment considers this effectiveness in more detail.

Comment 82

I have never developed information such as that in Tables 4 and 5, and so I can't speak to the reliability of these estimates. However, the assumption that heat lability is important is correct, as is the issue raised about concentrating a contaminant due to loss of moisture content (which depends on the style of cooking). I can also say that the *Salmonella* growth curves are appropriate, although my past experience is with poultry and dairy, not fish. Still, I can't see why the same equations/methods shouldn't apply for growth and de-activation. In poultry and dairy, however, one also must specify the temperature at which the product is stored, worked with, etc. That isn't done here, although the report needs at least some mention of where these factors appear inside (or are hidden inside) the growth equations.

I don't understand Table 6. I understand what it is intended to convey, but the numbers in it don't add up. I would presume that the number of catfish consumers (sixth column) times the mean number of servings per year (fifth column) would equal the annual servings (fourth columns). But they don't – not by a wide margin of 7. So I can't follow that table, or how it reflects in later calculations (output). I suppose the servings per year might be the average over the entire US population (I very much doubt it), in which case the table makes more sense.

Response 82

Temperature is included in the estimates based on the cooking style for the portion.

The reviewer's assumptions on the columns in table 6 are not valid because the distributions associated with this calculation (serving size, servings per month, etc.) are not normally distributed.

Comment 83

On Page 55, I note that a program aimed at Ictaluridae reduces the occurrence of disease better than one focused on the entire category of Siluriformes. This seems counter-intuitive, unless the authors are assuming a fixed number of inspections available (hence more resources are going to sampling non-Ictaluridae fish in the Siluriformes program, leaving the population more exposed to Ictaluridae exposure where the risk is concentrated). Whatever the reason, it needs to be explained.

Response 83

The comment is incorrect. Predicted reductions for Siluriformes are always larger than (or equal to) reductions for Ictaluridae (see Table 9).

Comment 84

H. Is the evaluation of uncertainties sound? I suppose so given that I am not convinced the uncertainty analysis plays any role in decisions to be taken here. I do, however, struggle to understand what one would do with the result where all assumptions are at their lower bound or all are at their upper bound. In order to be useful, there would need to be some explanation as to how likely either of these results is, something lacking in the current report. I agree, however, with decision not to attempt a fully nested uncertainty-variability assessment, as this would have been beyond available resources (but not beyond what might be expected in regulatory assessments where the goal is to understand actual risks, rather than to determine whether an inspection program is justified).

Response 84

As explained in the report, a probabilistic interpretation of the bounds of uncertainty that we estimate in the report is not possible. These can simply be interpreted as best/worst-case predictions. We agree with the commenter that more detailed uncertainty analysis was unnecessary for this risk assessment. So the initial approach will be applied to the revised document. Uncertainty analysis is intended to suggest how wrong the default predictions might be if (plausible) changes are made to the model inputs. The boundaries suggested by the original analysis were quite wide; the revised risk assessment considers predictions using public health surveillance as an alternative perspective regarding the plausible bounds of uncertainty.

Another purpose of uncertainty analysis is to identify data gaps that might be addressed in the future. In the revised risk assessment, we highlight the model input uncertainty. Because the model's predictions pertain to the future, however, the true number of illnesses and effectiveness of

FSIS inspection cannot be known prior to implementation of FSIS inspection.

Comment 85

I am similarly not sure what to do with the results in Section 6.2. A sensitivity analysis is often useful, but usually to help define how the uncertainty analysis will be performed. And then the uncertainty analysis is performed because one either wants to allocate resources to research (to reduce residual uncertainty) or to place the results in some sort of decision framework. Neither seems applicable here. I suppose Section 6.3, and its uncertainty analysis, is here to provide some insights into the reliability of the results in previous sections. Fair enough. But the authors don't give the reader insights into why the uncertainty analysis is being performed or what they intend the reader to do with the information. This could be improved.

Response 85

The sensitivity analysis was indeed completed to allow a more focused uncertainty analysis (that only considered the effects of the more sensitive model inputs). The uncertainty analysis might also be named a scenario analysis; it intends to explain how much higher or lower the model's outputs might be for combinations of extreme input settings in the model.

While the worst/best-case predictions can not be interpreted probabilistically, they are still useful in a decision framework. Absent any discussion of uncertainty, a decision simply hinges on a point estimate for cases avoided. This uncertainty analysis provides some idea about the boundaries of our predictions. These boundaries can, at least, inform decision-makers about the benefits that could accrue from the program.

The revised risk assessment provides a more detailed assessment of uncertainty. Nevertheless, the fact that it is impossible to be certain of the effectiveness of an FSIS inspection program prior to implementation, some uncertainty in the model predictions is unavoidable. This uncertainty cannot be informed by empiric evidence (either about human illness occurrence or specific effectiveness of various FSIS inspection procedures) because catfish-associated illnesses represent but a small share of human salmonellosis cases and an FSIS program for catfish is yet to be implemented. Therefore, improvements in certainty about program effectiveness will have to wait until data are collected upon implementation of the inspection program.

Comment 86

I agree, however, with the decision not to apply what the authors call a "second-order" uncertainty analysis, by which they mean a nested uncertainty-variability analysis. Such an analysis probably is infeasible given resources and data, and I am not convinced it would add anything to decisions. The lower and upper bound analysis used here is adequate. However, I believe the authors have used either ALL lower bound estimates, or

ALL upper bound estimates. I suppose there is some merit in doing this, but it would be highly unlikely that all of the parameters would be at their upper bound. A better approach would have been to sample randomly after assigning lower, mean and upper bound estimates of a parameter some likelihood (e.g. 10% for each of the lower and upper bounds, and 80% for the mean). I am also assuming that when the upper bound values were used, they were used for BOTH the before and after an inspection program calculations. If so, one could look at the predicted incidence of disease in the "before program" calculations and see whether they bear any resemblance to the incidence we currently see in catfish-consuming populations. I would bet they don't (greatly over-predicting that incidence). For example, are there REALLY almost a million cases of *Salmonella*-associated illnesses as shown in the final column of Table 11 (which must be assumed, otherwise how could the inspection program reduce the incidence by close to 700,000 cases)? I doubt it or no one would be eating catfish!

Response 86

Based on comments from public health surveillance experts (e.g., CDC), this assumption is on track with respect to the upper bound of uncertainty. It seems reasonable to expect that catfish-associated *Salmonella* illnesses are, even at the extreme, fewer than what can be attributed to more common food sources of salmonellosis (*e.g.*, chicken or beef). The revised risk assessment informs its upper bound estimates about human illnesses with this reasoning.

Comment 87

I realize the following is not strictly part of the uncertainty analysis, but it is a point about uncertainty I need to raise, and this is as good a place as any to include it. On page 45, I completely disagree with the description of the application of uncertainty factors (UFs). UFs do NOT reflect the "increased susceptibility" of humans. In fact, humans are sometimes more susceptible, sometimes less. UFs reflect this fact by reflecting the UNCERTAINTY as to whether humans will be more or less susceptible and/or sensitive for a particular compound where one can't be sure on the basis of other evidence. They are a way of building in a margin of safety, NOT a way of making the risk estimates better reflect the actual risk to humans. This paragraph needs to be re-written to reflect scientific understanding of the nature of UFs in regulatory decisions.
Because of this issue, I am concerned about the description of sampling from the UF distribution given on Page 46. There IS no distribution of UF values; the UF is developed from a distribution of susceptibility or sensitivity ratios for humans over rats. If any sampling is done, it needs to be between 0.1 and 10, not between 1 and 10, which seems to suggest that humans can be only MORE susceptible or sensitive than rats. This part of the assessment needs to be rethought.

Response 87

We would argue that our extrapolation of animal toxicity results to humans assumes that human susceptibility to chemicals was appropriate; however, as the revised risk assessment focuses on *Salmonella* such toxicity calculations are no longer considered.

Comment 88

The use of Equation 8 within this caveat is fine. There are many different distributional forms that could be used, and this one is as good as any other, as well as being employed often in risk assessments.

I am not sure what the figures on Pages 60 and 61 are intended to convey, or more properly why that information informs decisions. I suppose it is interesting to me scientifically, but I don't believe it says anything about the effect of the inspection program.

Response 88

Figures 3 and 4 illustrate the predicted annual variability in illnesses or cases avoided for *Salmonella* and cancer, respectively. The point of these figures is simply to illustrate that our predicted annual rates have an element of randomness in the real world. If the annual rate is constant, the realized number of illnesses/cases from year to year could follow a Poisson distribution. Such variability might be important in predicting the benefits accruing to the program as a function of time. For salmonellosis, the variability is minor relative to the average; for cancers, this variability is relatively substantive and could be included in a time-series analysis of costs and benefits. In any case, the revised risk assessment focuses on *Salmonella* and will not include this source of randomness in its predictions.

Comment 89

I. The more important hazards have been identified. I don't believe that adding in more hazards would change any central conclusions. It would increase the estimated incidence/risk, but my sense is that the current assessment already provides enough evidence of the desirability of an inspection program, and that increasing the number of hazards considered would not change this. This applies to both the chemical and microbial hazards examined. As to methods, I have already commented on these.

A very minor point, but Table 8 spells Acute as Accute.

Response 89

Upon careful consideration the risk assessment was revised to focus on *Salmonella.* The effects of other contaminants are no longer considered.

Comment 90

I also feel I should point out what I believe to be the correct methodology that should be used. This will not require significant changes to the EXCEL code I reviewed, but it does

require significant changes to how the methodology is described in the document. I propose:

1. A PDF of existing concentrations for a given contaminant is developed based on existing data (this is already executed correctly in the code, and described in the document).
2. A random selection is made from this PDF to obtain a concentration. This will be the "non inspection" value.
3. The result of 2 is multiplied by the post/pre inspection program ratio to obtain the expected concentration after the inspection program is in place. Ideally, this ratio would be developed based solely on data from the beef and poultry programs that apply to samples ABOVE A THRESHOLD LEVEL (since only these samples would be affected by an inspection program), and this ratio then applied only to catfish samples that are above the chosen threshold level, but I realize this may be asking too much of the existing data.
4. For EACH age/sex group considered, the concentrations in 2 and 3 are converted to total intake of contaminant in that serving (two results, one for pre and one for post inspection program; and then N sets of these two results – one set for each age-sex category).
5. For that contaminant, the concentrations are used to calculate the various risk metrics (cancer risk, IQ loss, HQ, etc) and the result stored.
6. The above 5 steps are repeated for a large sample population, perhaps 10,000 or more to gain stability.
7. For each contaminant, risk metric and age-sex category, calculate the MEAN value for probabilities and IQ loss, or the probability that an HQ value exceeds 1 (the first two are true means, the latter one is a frequency count).
8. The values of step 7 are multiplied by the total number of servings consumed each year to obtain the total number of effects in a year.

Response 90

This approach does not consider risk associated with exposure below regulatory levels or levels of concern. Risks associated with such exposures is likely greater than zero and should be included in the overall estimates.

8 REVIEWER NUMBER 5

Comment 91

General Observations and responses to the charge to peer reviewers

On the goals, accomplishments, and limitations of the assessment

First I might note that I am to some extent an outsider. My interests and experience have been in trying to make risk analysis a more effective and useful tool in managing hazards, especially in situations of considerable uncertainty; I am not, however, experienced in the details of food inspection. This limitation might be helpful, however, in giving a perspective on the transparency and balance in the presentation of the assessment. Some things that are obvious to those "in the know" are not so obvious to the rest of us. And very occasionally these raise significant issues that if left alone might receive inadequate attention.

The immediate goal of the analysis and presentation is to provide a robust assessment of anticipated benefits of a catfish inspection program that can be compared with the costs of the program to inform a decision (in this case a legislative mandate) to proceed to establish such a program. This goal could be interpreted rather narrowly: to identify and quantify a sufficient set of benefits to inform the decision. It could also be interpreted much more broadly: to develop a planning document that could help guide the realization of those benefits. While I have some quite significant technical reservations, I believe that the assessment and its documentation are largely successful in accomplishing the narrow mission. That is there are clearly identified anticipatable benefits whose quantitative assessment is believable and can be compared with anticipated costs. The pressures of legal mandates and time inevitably drive the agency toward maintaining a narrow focus and it would not be reasonable for me to expect a much broader planning document. However, a great deal of work has gone into this assessment and much valuable information has been compiled and built into the assessment model; it would be a pity to have that experience simply filed away and only used in so far as it is part of the experience of the creators of the assessment.

I believe that the addition of a modest amount of qualitative discussion along with some improvements in the documentation of the model would not be an undue burden and would contribute substantially to the future applicability of the modeling effort. And note the quote from the Charge to Reviewers under my specific comments to p. 10.

Response 91

The suggestion is appreciated and a qualitative discussion has been incorporated into the revised report as it pertains to *Salmonella.*

Comment 92

An interesting historical analogy is with the risk assessments for nuclear power plant accidents. These landmarks in the early days of risk assessment were originally developed to inform the debate on liability for nuclear accidents (associated with the renewal of the Price-Anderson act); however, we have learned subsequently that their most important contribution has been to provide guidance for substantial improvements in nuclear plant safety.

For the case at hand, the important observation is that there are many potential benefits to an inspection program that are not easily or appropriately quantifiable and these include opportunities to better address many issues that arise in considering uncertainties in the quantification effort. A qualitative discussion might consider the opportunities provided by obtaining better knowledge of the distribution of contaminants, better evaluation of the effectiveness of the inspection system, identifying opportunities to make and test improvements in the inspection program, and better preparation for new contamination concerns as they arise. In addition a qualitative discussion could pay attention to some of the indirect benefits of an inspection system: avoidance or mitigation of public anxiety and economic losses from contamination incidents (the social amplification of risk); improving public health by encouraging more consumption of fish – particularly fish that is relatively low in contaminants like mercury; etc.

Response 92

The revised risk assessment includes substantial qualitative discussion regarding program effectiveness. Nevertheless, we anticipate the greatest opportunity will occur once a program is in place and data are generated from it. We expect the risk assessment approach will be used to refine and improve the inspection program in the future.

Comment 93

The identification of opportunities for improving the benefits of an inspection program over time should be a (modest) part of the discussion in the scope of the assessment (section 2.2) and in setting the stage on risk management (section 2.3) and the risk assessment (section 2.4). It should also be a modest part of the discussion of the prediction of regulatory effects (section 6.1), sensitivity analysis (section 6.2), and uncertainty analysis (section 6.3), and it should be part of the summary (section 7). Further below I point out some specific pages where such observations would fit.

Response 93

The revised risk assessment includes more discussion about an inspection program. Nevertheless, a risk assessment should focus its analysis on its intended purpose. In this case, the risk assessment primarily informs Agency rule-making and is used to assess predicted benefits of a yet-to-be-implemented FSIS inspection program.

Comment 94
In addition there is room for improvement of the documentation within the crystal ball spread sheet model. More thorough and consistent documentation of the data being used, the data sources (and alternatives) and the assumptions made in the various steps in the actual spread sheets, would make the model easier to expand and update.

Response 94

We have addressed the need for improved documentation with respect to *Salmonella* in the revised risk assessment report.

Comment 95
An important aspect of the assessment is that it explicitly compares management alternatives. This desirable characteristic is why we should be concerned with the ongoing use of the assessment and the practical implementation of management policies. In that context the use of Figure 1 to describe the organization of the assessment is perhaps not best as management (and the research needed to evaluate and improve management actions) is pushed too much to the side. A good alternative that considers this concern but maintains much of the original red book spirit is given in the recent NAS report *Science and Decisions: Advancing Risk Assessment* (NRC 2009) as both Figure S-1 (from the report summary), and 8-1; the assessment authors may enjoy reading chapter 8 as well. There is a similar problem with Figure 2 in the assessment. It gives the structure for the baseline analysis, but obscures the role that inspections can play and a little bit of editing of that figure might be helpful (or at least some clarifying discussion). As the assessment notes, and I will comment on later, there really are 4 options considered because the possibility of inspecting or not inspecting imported catfish is evaluated within the model. There is only very limited discussion of the relative merits and difficulties of including imported catfish in the text and that should be remedied.

Response 95

The factors mentioned by this reviewer will be considered by the appropriate FSIS policy makers.

Comment 96
Technical reservations and a comment on hazard identification

I mentioned that I had some reservations concerning the model in its present form. Some of these I note as specific comments directed at the discussion on particular pages of the document, but there are three recurring issues that I want to mention up front along with a general comment on the selection of hazards for analysis.

- Over-reliance on and lack of critical discussion of the Pareto distribution I try not to be very fussy about the choice of distributions for Monte Carlo analyses, particularly when the effect of the distribution is largely an interpolation from a fit to data. And the fact that there is not much of a mechanistic justification for its use (compared to a log normal distribution for instance) does not seem so serious since at the high end of values the arguments for log-normality become weak and power laws often make a good fit. However, there are several problems with the use of Pareto distributions here and they merit, at a minimum, a careful critical examination. From my perspective, the most significant issues are with low values. The structure assumed in the model is that there is generally a finite probability of zero contamination, then zero probability for contamination up to some level (perhaps a detection limit, but this is not clear from either the text or the spreadsheet, nor is it consistent between the domestic and international distributions), and then a finite declining probability for contamination above the particular level. In many cases, most of the probability resides quite close to the specified level, while the expected values (the means) reside well higher on the tail of the distribution. (Indeed for some of the distributions, the means are infinite implying a large (infinite?) contribution to the expected health effects if there were sufficiently many trials; that can be viewed mostly as a mathematical peculiarity, but it also is a warning.) The problem at the low levels is that this picture of a gap is not realistic (especially for common contaminants like lead and arsenic), and there are practical management issues that depend on what happens on both sides of the detection limit. Do the catfish farmers in responding to the implementation of an inspection system only alter the likelihood of detection (increase a probability of zero lead, not that that is practical) or do they effectively move a distribution of contamination to a lower level? If the latter there are likely to be further benefits from the lowering of undetected lead levels. Another way to think about this management question is to consider the potential value of improving detection limits.

Response 96

The comment is well taken. Yet, the effect of some other distributional form is unlikely to change the general conclusions of the model; the predicted effects of FSIS inspection on hazards other than *Salmonella* are relatively minor. The revised risk assessment focuses solely on *Salmonella*. The focus on *Salmonella* does not rely on a Pareto distribution assumption.

Comment 97

- Imperfect characterization of inter-individual variability including variability in background levels of exposure For some of the harmful effects considered,

cancers and IQ deficiencies (for the assumed dose-response models) the per meal analysis and simulation works fine; the risks are additive and distributed across the population (or identified population subgroups). But there are non-linearities in the dose response for chronic diseases such as cardiovascular diseases and extreme non linearity for acute toxicity (though this may still not give many or any cases). There is interindividual variability in the sensitivity to such exposures and that is tied to a person, not a meal, and there is also interindividual variability in background levels of lead in blood for instance. (some of that variability is age dependent – older people are likely to have significantly higher blood lead concentrations because of accumulations in their bones). Distributions reflecting variability in both sensitivity and background should be considered along with the possibility that a particular individual can consume a relatively high number of catfish meals. For acute toxicity, the possibility of concern is a sensitive individual who eats several servings worth of highly contaminated catfish in a relatively short period of time. This possibility might well not be of practical significance, but the analysis to show that is obscured by a per meal analysis that confounds the Price et al. uncertainties in extrapolation with the inter-individual variability in sensitivity and that should be clarified. Incidentally, there is a good discussion of alternative approaches to dose response in Chapter 5 of the NAS *Science and Decisions* report mentioned above.

Response 97

In conducting risk assessments for rulemaking, as we are doing in this case, it is appropriate for us to concentrate on the overall probability of illness in the population. Benefits are computed across the totality of cases and severity is assumed to be independent of the probability of illness (*e.g.*, the severity of *Salmonella* illness is assumed independent of the dose that caused the illness). Therefore, the risk assessment essentially predicts the "average" probability of illness per serving, and then multiplies this probability by the number of servings (per annum) to determine the number of illnesses (per annum). The difference in illnesses between the baseline and post-policy scenarios determines the number of cases avoided. A benefit-per-case-avoided is assigned to determine total benefits accruing to the policy.

Comment 98

- Combining in a Monte Carlo simulation stochastic responses, probability distributions to characterize variability and probability distributions to characterize uncertainty can obscure the identification of opportunities for improving the management of hazards. Here too the NAS *Science and Decisions* is a good resource – chapter 4 provides an abbreviated update of the discussion in the 1994 NAS report *Science and Judgment in Risk Assessment,* though the latter is also worth consulting. From a management perspective the practical concern is that new information can reduce uncertainty and enable

better decisions and better focusing of effort, while new information will not reduce variability, but might delineate it better and suggest ways of targeting management actions. Thus, generally speaking, it is cleaner not to include uncertainty distributions in Monte Carlo simulations unless you are specifically using the simulation to reflect the uncertainty. Since I believe the authors of the assessment have taken an appropriate approach by characterizing uncertainties qualitatively with the presentation of results from sensitivity analyses, including uncertainty distributions in the primary (best estimate) simulations serves only to create an additional blurring of the findings. Some examples are the distribution of effectiveness of FSIS programs (it is better to learn about effectiveness), and uncertainties in parameters describing dose response.

Response 98

We agree with this comment. The inclusion of uncertainty about effectiveness and dose-response parameters was inadvertent. The revised risk assessment considers uncertainty about effectiveness, but makes different predictions for specific levels of effectiveness. Nevertheless, the uncertainty included in the original risk assessment's default predictions did not substantially influence the conclusions because that uncertainty distribution was averaged across all servings.

Comment 99

- The selection of hazards The prioritization approach to select hazards for analysis seems appropriate and done with care. I want to mention that usefulness for future management does add some further considerations. For instance, I would have liked to have seen at least one more microbial hazard, because a comparison with the issues pertaining with *Salmonella* might be informative. And public concerns matter: I was surprised not to see Dioxin in the list, given that there has been a catfish incident involving dioxin. But most important is the qualitative aspect which should be stressed in the final discussion. At the beginning of section 3, the authors properly observe that the knowledge base (and aquaculture practice) may change: one of the beneficial opportunities provided by inspections is the capability to keep track of and evaluate such changes.

Response 99

The revised risk assessment focuses on *Salmonella* and the effects of other contaminants, including dioxin, are no longer considered. We lack human illness data associated with catfish consumption that would support the inclusion of additional microbial hazards to the high priority group.

Comment 100

Comments on model documentation

1) Is the report clearly written?

The report is quite well written and easy to follow (a great help to the reviewer and future readers) – there are places noted below where explanations assume too much prior knowledge

2) Does it completely cover all aspects of the analyses?

There some significant gaps as discussed above and identified in the specific page comments below.

3) **Does it follow a logical structure and layout?**

The structure and layout are logical and clear – however as discussed above (and in specifics below) the structure has been too much drawn from the old red book (NRC 1983) and downplays the importance of critical analysis of the effects and effectiveness of inspection.

Response 100

The revised risk assessment will provide more detail regarding the anticipated public health impact of FSIS' inspection program based on how effective this program might be and the timeframe in which it takes FSIS to achieve this "effectiveness" (i.e.., to achieve a percent reduction in *Salmonella* prevalence on catfish and corresponding reduction in annual cases of salmonellosis in the U.S. each year).

Comment 101

6) **Where data are included/excluded, does the documentation provide adequate justification?**

Most choices are justified – there is room for some improvement as noted below.

Comment on the validity of the model

a. Are these assumptions logical and adequately justified?

As noted above, I have some significant reservations about the assumptions in the model and these should be addressed. These include the per meal approach for some of the hazards as discussed above. Some further issues and additional detail are mentioned with specific page references below

b. **Is the selection of data appropriate?**

Yes, with some reservations below.

c. **Are model outputs reasonable?**

The basic findings seem plausible. Some aspects should be checked: for instance the chronic disease and acute toxicity findings which depend on interindividual variability and the implications of using Pareto distributions. In these cases my expectation is that there has been an underestimate of potential benefits

Response 101

See response to q 16. The revised risk assessment focuses solely on *Salmonella*. That pathogen does not rely on a Pareto distribution assumption.

Comment 102

d. Is the evaluation of uncertainties sound?

The basic approach using sensitivities is sound, provided it is coupled with a more complete qualitative discussion. As noted above, some uncertainty is put into the Monte Carlo and that is confusing. And there are some important gaps in the discussion as noted below.

Response 102

We have included an expanded qualitative discussion of uncertainty in the revised risk assessment.

Comment 103

Comment on the risk assessment model

a. Chemical Hazards

I discussed identification above: there are some minor points mentioned below. The per-meal approach only is valid for some outcomes.

b. Microbial Hazard

As noted above I would have liked to see one other microbial hazard for comparative purposes even though the others were only assigned medium priority. Also given the large impact of *Salmonella*, it might well be that medium priority hazards are significant. The per meal approach seems appropriate for microbial hazard

Response 103

We lack additional human illness data associated with catfish consumption to support the inclusion of microbial hazards other than *Salmonella*. See McCoy et al (2011) JFP 74(3)500-516) for a discussion of foodborne agents associated with the consumption of aquaculture catfish.

Comment 104

Specific Observations

Executive Summary

p.10 It might be worth quoting the beginning of the Charge to Reviewers especially if the future use of this assessment is contemplated.

The Food Safety and Inspection Service (FSIS) Office of Public Health Science (OPHS) addresses food hazards through prevention and control activities. Risk assessments are used to evaluate intervention strategies to reduce foodborne risks and to guide, support, and enhance the agency's overall decision-making process, risk-management policies, outreach efforts, data collection initiatives, and research priorities.
p. 11,12 The executive summary should clarify that there are really four scenarios discussed and, preferably, should reflect some further discussion from a revised text that explains why all are considered and what the implications are.
p.13 There should be some reflection of the (revised and extended) summary

Response 104

We appreciate these comments and have revised the executive summary to be more informative. The purpose of the risk assessment is to provide a foundation for policy development. As such, during the risk assessment process, minimal assumptions about the implications of the various policy options under consideration are included in reports such as this.

Comment 105

Introduction
p.14 Here again you could look toward the future with the Charge to Reviewer's quote
p.15 Under Scope need more discussion of what the key issues are, what is and what isn't in the assessment, and, something, about how an inspection program creates opportunities for reducing hazards and these can change and be improved over time.
p. 16,17 Under Risk Management need some discussion of what management can accomplish and how it gets put into an assessment model; also some of the qualitative discussion of opportunities for adapting management by gathering new information and adjusting policies accordingly. And there must be more discussion of the merits and justification for considering both imports and domestic inspections.

Response 105

The reviewer's comments have been taken into consideration in the drafting of the revised risk assessment report.

Comment 106

p.17 Under Risk Assessment, as I noted above, I recommend a different Fig. 1 and that you say something about the modern perspective on risk assessments that it is useful to consider management options. In addition there should be a bit more discussion of the purposes of prioritization (making the assessment more tractable, and, perhaps, guiding the testing program)

Response 106

We have made the suggested changes in the revised report.

Comment 107

p.18 Here you could mention interindividual variability and variability in background and either here or in Model overview a mention of uncertainty characterization

Response 107

This variability information has been included in revised report.

Comment 108

p.19 Under Model overview I've noted that Fig 2 could be edited or, at least, the discussion could draw attention to the importance of inspection effects and effectiveness on the model.

Response 108

We appreciate the reviewer's comment and we have made the suggested changes in the revised report.

Comment 109

p.19,20 Some refinement in the statements about per meal analysis is needed.

Response 109

This was addressed in the response to Comment 67.

Comment 110

p.22 In Model inputs, continuing from the discussion of Figure 2 some discussion of the input on regulatory analysis would be helpful. (incidentally it was not easy for me – an outsider effect to track down the ref to the change from 1994 to 2008) I think you have a good case for assuming that you could do as well for *Salmonella* in catfish as good practice for the other products, but I'd like some discussion of trends and whether the expected level of contamination affects your expectations. Also I think it is a much more open question whether the same sort of results apply to chemicals. And finally there is the question about whether for chemicals the inspections increase the probability of zero contamination or reduce the amount of high contamination.

Response 110

We agree with this comment. The revised risk assessment includes more discussion of program effectiveness, and as previously mentioned, focuses on *Salmonella* only (see also Response 1).

Comment 111

P22,23 For model outputs, I do wonder why chronic effects of Arsenic were not considered along with lead.

Response 111

As previously mentioned (Response 14), we were limited to effects and chemicals for which dose-response functions can be derived. The revised risk assessment focuses on *Salmonella* only.

Comment 112

Hazard Identification

p.23 I like the opening paragraph; it represents a good introduction to the kind of adaptive approach to management that we can expect of food inspection and that is now called for in contemporary risk assessment.

p.24 As noted above, I wonder why Dioxins aren't included given that there was a significant episode with catfish and dioxin.

Response 112

For reasons presented elsewhere (e.g. response 113), the revised risk assessment focuses on *Salmonella* only

Comment 113

p.25-27 Regarding prioritization of chemicals – I'd like a bit more qualitative discussion of the prioritization scheme (right now it seems too "insidery"). What were the ingredients and how was it done. Perhaps a box showing an example or two would work. And the list could be made into a more compact Table.

p.28 And the same goes for microbial prioritization

Response 113

The initial draft risk assessment predicted – across all of the hazards considered – that *Salmonella* illnesses were the most frequent adverse human health occurrences. The revised risk assessment focuses exclusively on public health risk from *Salmonella* associated with the consumption of catfish.

Comment 114

Exposure Assessment

p.30 Here we get into the issues of per meal exposure and Equation 3 raises the issue posed by the use of Pareto distributions – is prevalence some amount of contamination or only contamination above a level of detection?

Response 114

Prevalence is contamination above level of detection. This has been clarified in the updated report.

Comment 115

p.31 The Pareto fits require more (and better) justification

Response 115

Justification was provided in the original report. Also, see Response 16 and Response 96.

Comment 116
p.32 The nitrofurans discussion is another example of opportunities for adaptation

Response 116
Nitrofurans are not part of the revised risk assessment, which focuses on *Salmonella*.

Comment 117
p.33 I think more discussion is needed of the inorganic fraction of Arsenic (I wonder if that one paper (Li et al) really covers the range of possibilities); I assume the use of the triangular distribution is intended to reflect variability in the ratio; but perhaps more uncertainty should be considered at the end.

Response 117
Use of the distribution attempts to address the variability in the ratio of organic: inorganic arsenic. Again, this is not part of the revised risk assessment, which focuses on *Salmonella*.

Comment 118
p.34 Among the Pareto distribution mysteries is why the minimum level differs between imports and domestic contamination. And the infinite means are disturbing and merit a comment if you don't reanalyze them.

Response 118
This is a reasonable comment; however the revised risk assessment focuses solely on *Salmonella*. In our estimates for Salmonella, we do not rely on a Pareto distribution assumption.

Comment 119
p.39 Regarding catfish consumption, more discussion is needed of how you balance NHANES numbers with NMFS numbers – there appears to be an inconsistency between the last three items in the table – and you should just say which #s you use for what. What would be interesting also is some discussion of trends – I suspect there has been an increase in catfish production/eating and it would be worth thinking about whether that is enough to affect the design of a program going forward.

Response 119
Table 6 has been revised to reflect changes in the revised draft risk assessment. The NMFS data was replaced with 2008 NASS catfish production data, because the NMFS data were out of date. In the original table 6 annual catfish servings were estimated by dividing the annual NMFS catfish production by the NHANES estimated mean serving size.

The idealized mean number of servings per year in the next column were estimated by dividing the annual number of catfish servings by the maximum estimated number of US catfish consumers from NHANES data. The last column in the table representing the actual number of catfish consumers used in the risk model is the estimated percent of annual catfish consumers multiplied by the total expected US population.

When we examined the 8 years of NHANES data for catfish consumers using the single 24-hour recall variable, which was consistent over the 8 years we were able to show that the percentage of catfish consumers evaluated at the four two-year survey release dates showed an increasing trend from 1999 through 2004. The percentages of the total 249 subjects were in order: 19.3%, 30.5%, 32.9%, and 17.3%. The trend was not significant because the last two-year period showed a decrease. The next release of data for 2007-2008 should be available soon and should provide new information on the catfish consumption trend.

Comment 120

p.40,41 Also the NHANES data suggest that there are high frequency catfish consumers the large proportion who have eaten a catfish meal in the last day. This should be accounted for as variability in consumption.

Response 120

This consumption variability is addressed in the uncertainty analyses.

Comment 121

p.43 The use of Table 7 merits reconsideration. At issue is whether for body weight you want to assume that catfish eaters differ from the rest of the population. You could make an argument for that, based on these data, but the samples, once sub-divided aren't very large. A reasonable compromise might be to use those means but to use standardized standard deviations

Response 121

We chose to use the bodyweight distributions for the 1996-2006 NHANES respondents.

Comment 122

Hazard Characterization (Dose-Response)

p.44 equation 6 is ok, provided that we have dealt with the possibility of multiple servings for acute hazards and variabilities for chronic disease

p45,46 Under acute mortality need to rewrite to clarify the difference between uncertainty factors and variability in sensitivity

Response 122

This comment is confusing – it may have stemmed from terminology differences used in the risk assessment and the toxicology fields. We believe the diction used in the report is consistent with standard risk assessment terminology.

Comment 123

p.49,50 Needs rewriting to consider non-linearity and interindividual variability in sensitivity and background levels

Response 123

Quantitative chemical analysis is no longer part of the updated report.

Comment 124

Risk Characterization

p.51-53 Here the text needs to take account of the previous reservations on non-linearities and distributions

Response 124

Clarification of these matters is provided in the revised risk assessment.

Comment 125

p.55 The discussion of imports and domestic effects should be clarified.

Response 125

Clarification of these matters is provided in the revised risk assessment.

Comment 126

p.73 I agree with the justifications for doing uncertainty by sensitivity. But I would have liked also a bit more qualitative discussion of model uncertainty, the uncertainty in choice of data sets, and the issue of the uniformity of inspection effect.

Response 126

Additional quantitative discussion has been added to the revised risk assessment.

Comment 127

Summary

p.78 It would be desirable to have a more comprehensive conclusion including qualitative opportunities for improving the knowledge base, improving effectiveness of inspection programs, and more effective use of risk approaches in evaluation and adaptation.

Response 127

The revised risk assessment includes more discussion about use of a risk assessment model to support future decisions as data are generated by the inspection program.