Assessment of the Potential Change in Human Health Risk associated with Applying Inspection to Fish of the order Siluriformes

Prepared by the

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Food Safety and Inspection Service

United States Department of Agriculture

January 2015

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Acknowledgements

Completion of this risk assessment was facilitated by constructive comments, suggestions, and data provided by experts from the following agencies and academic institutions: the U.S. Department of Agriculture's, Food Safety Inspection Service, Office of Budget and Program Analysis, Office of Risk Assessment and Cost-Benefit Analysis, Agricultural Research Service, Agricultural Marketing Service and Office of Catfish Inspection Programs; the U.S. Department of Health and Human Services', U.S. Food and Drug Administration's (FDA's) Center for Food Safety and Applied Nutrition's, and Center for Veterinary Medicine; the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; the U.S. Department of Commerce, National Oceanic and Atmospheric Administration; the Environmental Protection Agency; the Minnesota State Health Department; the University of Arkansas, Pine Bluff; Colorado State University; Johns Hopkins University; Mississippi State University, and Texas A&M University.

We are grateful to the following individuals: Linda Abbot,[5] Cade Akers,[6] Patty Bennett,[7] Quita Bowman Blackwell,[7] Sid Clemans,[8] Kerry Dearfield,[7] Philip Derfler,[7] Carole R. Engle,[9] Denise Eblen,[2] Emilio Esteban,[7] David Goldman,[7] Elisabeth Hagen,[7] John Hicks,[7] Larry D'Hoostelaere,[10] Janell Kause,[2] Kelly Kovich,[25] Heejeong Latimer[2] Carol Maczka,[7] Patrick McCaskey,[7] Otis Miller[7] William Milton, Jr.,[7] Doritza Pagan-Rodriguez[2] Mark Powell,[7] George Salem,[10] Carl J. Sciacchitano,[10] James Schaub,[5] Carl Schroeder,[7] William Shaw[7], Zachary Shirley,[11] Juan Silva,[12] Alice Thaler,[7] James Wilkus,[7] Charles Williams,[7] Ray Yang.[13]

We acknowledge and thank: Dare Akingbade,[2] Tracy Ayers,[14] Mark Briggs,[15] Mary Carson,[10] Lynn Cruickshank,[7] Thaddeus Graczyk,[16] Tim Hansen,[17] Karen Herman,[14]

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We also thank Peter Bridgeman,[7] Diana Haynes,[18] Sherri Johnson,[7] Mike Kelley,[7] Davonna Koebrick,[19] Jo (Dyer) Kraemer,[18] Andrew Maccabe,[14] Gregory McMillon,[20] Michael P. Masser,[21] David Soderberg,[22] Christopher Sommers,[23] Isaac Gene Sterling,[18] Granvil Treece,[21] Rasika Tripathy,[7] Sherri B Turnipseed,[10] Patricia W. Varner,[21] and Steven Wilson,[17] and Peter Woods.[24]

Notwithstanding the considerable help and valuable expertise provided by the abovementioned, responsibility for the content of this report rests solely with the U.S. Department of Agriculture' Food Safety and Inspection Service.

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Executive Summary

The Food, Conservation, and Energy Act of 2008 (Public Law 110-246, §10016(b)), known as the 2008 Farm Bill, amended the Federal Meat Inspection Act (FMIA) to provide that "catfish, as defined by the Secretary," is an amenable species under the FMIA. On February 7, 2014, the Agricultural Act of 2014 (Pub. L. 113-79, Sec. 12106), known as the 2014 Farm Bill, amended Section 1(w) of the FMIA to remove the phrase "catfish, as defined by the Secretary," and replace it with "all fish of the order Siluriformes," thus including these fish among the amenable species (21 U.S.C. 601(w)(2)). Hereafter in this risk assessment, the term "catfish," defined in proposed 9 CFR 531, and used throughout this text, is replaced by the term "fish of the order Siluriformes," "Siluriformes fish," or simply "fish," understood to mean any fish of the order Siluriformes, with the following exceptions:

1. when discussing original publications and reference sources that specifically use the term catfish or other specific subsets of Siluriformes or other fish; and
2. when the risks from a specific subset of Siluriformes are being discussed.

The USDA Food Safety and Inspection Service (FSIS) considers it useful in the context of this rulemaking to attempt to quantify the microbiological risk associated with consuming farm-raised Siluriformes in the United States. However, limited information on the extent of microbial contamination and chemical residues on Siluriformes limit our ability to make strong statements about the baseline risk. Furthermore, the lack of experience with implementing the inspection program associated with this rulemaking in the context of aquaculture makes estimating the impact of such a program on any baseline risk difficult. As such, the assessment FSIS presents here simply provides insight into the potential risk reductions that might accompany the implementation of the type of inspection program used for poultry (i.e., broiler) in the U.S. This report also identifies potential chemical and microbial hazards. Once implemented, the inspection program will generate data on whether there are concentrations of chemical and microbial hazards present in these fish, and thus whether the inspection program is actually changing risks to consumers.

This risk assessment focuses on exposure to *Salmonella* because a broad hazard identification study identified *Salmonella* as one of the few potential hazards that there was sufficient data to assess in Siluriformes. This risk assessment provides different scenarios for the benefits that might result from an inspection system in Siluriformes similar to FSIS' inspection system for poultry. We are particularly interested in *Salmonella* because the general burden of illness from this pathogen in the U.S. remains a concern. We also note that there is evidence that at least one outbreak of human salmonellosis may have been related to Siluriformes consumption. FSIS acknowledges, however, that applying its empirical evidence describing the effectiveness of an FSIS inspection program for *Salmonella* control in another regulated species (i.e., poultry) carries with it significant limitations.

The objectives of this risk assessment are:

1) To estimate the annual numbers of human salmonellosis cases from Siluriformes.
2) To estimate the potential number of cases that might be avoided following implementation of an FSIS inspection program.
3) To compare these estimates with those based on to public health surveillance evidence.
4) To explore the sensitivity of these estimates to different modeling assumptions.
5) To characterize some aspects of the uncertainty surrounding these risk assessment model estimates.

The risk assessment focuses on catfish within the order Siluriformes, but also includes an analysis of catfish defined more narrowly as Ictaluridae. The risk assessment uses statistical models to estimate human illnesses that might be associated with catfish and the illness cases that might be avoided by implementing an FSIS inspection program. When modeling the potential effects of an FSIS inspection program, the assessment assumes that the Siluriformes inspection system would be similar to the system FSIS uses for poultry. The risk assessment model uses Monte Carlo techniques to combine the random variables that estimate exposures for four different exposure classes, which include the most common ways catfish (of the order Siluriformes) is prepared in the United States. There are four key assumptions underlying the risk assessment model:

1) Estimates of the current level of *Salmonella* contamination on Siluriformes
    - *Salmonella* contamination data from poultry were used as surrogates for Siluriformes contamination
    - The same data (from poultry) were used for both import and domestic Siluriformes
    - Catfish (of the order Siluriformes) handling during retail and home storage was considered independent of the initial *Salmonella* concentration on the fish carcass.
2) Estimated amount of catfish (of the order Siluriformes) consumption in the US
    - Each fish serving was derived from a single carcass.
3) Modeled estimates of illness incidence
    - Incidence of salmonellosis cases was estimated using WHO/FAO's dose-response relationship
4) Potential levels of effectiveness associated with the FSIS inspection program
    - Empirical data on program effectiveness for FSIS poultry inspection (i.e. broilers) was used.

The assumptions listed above and the quality of available data introduce substantial uncertainty both the estimated baseline number of salmonellosis cases attributable to catfish (of the order Siluriformes) consumption. The modeled lower and upper bound scenarios suggest estimates between 100 and 6,200 salmonellosis cases might be associated with catfish (of the order Siluriformes) consumption annually.

The 2014 Farm Bill defined catfish as all fish in the order Siluriformes, whereas another definition considered during the proposal included only fish within the Ictaluridae family, which are the subset most commonly sold in the United States. This risk assessment estimates an annual average of 2,308 salmonellosis cases that may be from Siluriformes as defined in the 2014 Farm Bill, with an annual average of 1,764 of those salmonellosis cases potentially attributable to Ictaluridae. These estimates seem consistent with a different estimate that we modeled based on the limited data available from the Department of Health and Human Services' Centers for Disease Control and Prevention (CDC) regarding outbreaks that may have been associated with these fish. Regardless of whether considering Siluriformes or Ictaluridae, the model estimates an average probability of illness of 1.5×10^{-6} salmonellosis cases per serving, though this number could be substantially lower because our baseline information on the rate of contamination is limited. This probability incorporates the estimated prevalence of contaminated servings and suggests that *Salmonella* illness from these fish is an uncommon event.

There is substantial uncertainty regarding the effectiveness of a future FSIS inspection program aimed at reducing the estimated prevalence of *Salmonella*-contaminated Siluriformes, and different levels of effectiveness yield different levels of benefit. To better serve as a decision tool, this risk assessment models a range of assumptions – from 10% to 90% inspection program effectiveness – to estimate public health benefit outcomes. For example, if an FSIS inspection program is 50% effective within a 5-year timeframe, model estimates of between approximately 50 and 3,100 *Salmonella* illnesses prevented annually using the Siluriformes definition.

As noted above, the risk reduction estimates are subject to substantial uncertainty regarding both the estimated baseline number of salmonellosis cases attributable to catfish (of the order Siluriformes) consumption and the extent to which the experience associated with controlling *Salmonella* in poultry is applicable to controlling *Salmonella* in Siluriformes. Once the FSIS inspection program is in place, however, the data generated will allow the Agency to further address the effect of inspection on chemical hazards and other microbial hazards (in addition to *Salmonella)* that can cause adverse human health outcomes associated with the consumption of farm raised Siluriformes.

1. Introduction

This risk assessment is designed to meet the following objectives:

1) To estimate the annual numbers of human salmonellosis cases from Siluriformes
2) To estimate the potential number of cases that might be avoided following implementation of an FSIS inspection program
3) To compare these estimates with those based on to public health surveillance evidence
4) To explore the sensitivity of these estimates to different modeling assumptions
5) To characterize some aspects of the uncertainty surrounding these risk assessment model estimates

The risk assessment focuses on catfish within the order Siluriformes, but also includes an analysis of catfish defined more narrowly as Ictaluridae. The risk assessment uses statistical models to estimate human illnesses that might be associated with catfish and the illness cases that might be avoided by implementing an FSIS inspection program. This risk assessment provides a range of estimates of the differential effect of introducing a Food Safety and Inspection Service (FSIS) Siluriformes inspection program on the potential number of human *Salmonella* illnesses from consumption of farm-raised catfish of the order Siluriformes each year.

This risk assessment model estimates the potential change in risk associated with implementing an FSIS inspection program for farm-raised Siluriformes that is similar to that used for poultry. Incorporated into the model was the consideration of two different potential definitions of these fish. The definition of these fish that is consistent with the 2002 Farm Bill[25] is specific to the family Ictaluridae, native to North America. There are additional families of fish on the commercial market in the order Siluriformes, where the North American family Ictaluridae resides. On February 7, 2014, however, the Agricultural Act of 2014 (Pub. L. 113-79, Sec. 12106), known as the 2014 Farm Bill, amended Section 1(w) of the FMIA to remove the phrase "catfish, as defined by the Secretary," and replace it with "all fish of the order Siluriformes," thus including these fish among the amenable species (21 U.S.C. 601(w)(2)). Therefore, an evaluation of potential change in risk associated with using the Ictaluridae definition of "catfish"

[25] Farm Security and Rural Investment Act of 2002, known as the 2002 Farm Bill, amended the Federal Food, Drug, and Cosmetic Act (21 United States Code §§ 321d(a), 343(t); Public Law 107-171, Title X, §10806, 116 Statute 526).

represents a different range of exposure to that of the Siluriformes definition for "catfish". This risk assessment generates an estimate of the underlying public health risks resulting from exposure to *Salmonella* for both Siluriformes and Ictaluridae, as well as how that risk might be reduced through implementation of an inspection program.

Chapter 2 and the Addendum provide the hazard identification for Siluriformes by cataloging chemical and other microbiological hazards that have been found in some other types of seafood or aquaculture and, thus, have the potential to be present in Siluriformes. They also summarize available data on chemical residues in catfish and information from Centers for Disease Control and Prevention's (CDC's) outbreak database[26]. The remainder of this risk assessment report describes the quantitative modeling approach used for the analysis of potential *Salmonella* contamination. The choice of *Salmonella* as a microbial hazard of potential concern is outlined in Chapter 2.

After discussing the hazard identification in Chapter 2, the remainder of the report focuses on *Salmonella* and is divided into four sections: 1) an overview section that explains the conceptual model and its mathematical structure; 2) an exposure assessment section that explains the modeling inputs used to estimate potential exposures of humans to *Salmonella* in catfish (of the order Siluriformes) servings; 3) a hazard characterization section introduces the dose-response relationship used to estimate the probability of illness per *Salmonella*-contaminated catfish (of the order Siluriformes) serving; and 4) a risk characterization section combines the exposure assessment with the hazard characterization.

[26] Testing data are from the US Department of Agriculture's (USDA's) Agricultural Marketing Service (AMS) and Food Safety and Inspection Service (FSIS), and the FDA tested between 2001 and 2010.

2. Hazard Identification

This section constitutes the hazard identification for this risk assessment. It begins with a discussion of potential microbial hazards in farmed fish and a summary of information available on contamination of Siluriformes. That is followed by a discussion of potential chemical hazards, which are identified through consideration of aquaculture and processing practices, as well as environmental factors. The last subsection summarizes the available data on residues detected in catfish samples tested by the Agricultural Marketing Service (AMS), US Food and Drug Administration (FDA) and the Food Safety and Inspection Service (FSIS). Although there is limited data on the chemicals present in Siluriformes, this hazard identification does put the potential microbial contamination—and the decision to focus this risk assessment on *Salmonella*—in the overall context of range of potential hazards in Siluriformes and the limited information available on those hazards in Siluriformes.

2.1 Prioritization of Potential Microbial Hazards

Several bacterial pathogens have been associated with farmed fish (Ramos and Lyon, 2000). Because fish is typically cooked prior to consumption, Siluriformes-associated microbes do not routinely present problems of public health concern (Engle et al., 2009). Therefore, defining specific microbiological hazards based on historical trends is a challenge with Siluriformes because the pathogen-product pair relationships are not well established through epidemiological data. For these reasons, the microbial hazard identification was general to foodborne and waterborne pathogens potentially associated with fresh-water fish products.

Pathogens of potential concern were categorized based on a combination of findings from literature reviews and fish-associated outbreak information obtained from the Centers for Disease Control and Prevention (CDC) into two priority groups (higher and lower – acknowledging that even the "higher" priority group may have an absolute risk which is low). Categorization was based on microbial association with the water in which fish are raised, the fish themselves and the final product, and also with the potential of the microorganisms to cause adverse public health effects if consumed.

Hazards are further delineated in terms of their potential relevance to raw or ready-to-eat (RTE) Siluriformes (*i.e.*, the relevant pathogen-product pairs).

For illustrative purposes, the subsequent steps (exposure assessment, hazard characterization (dose-response) and risk characterization) in this risk assessment were applied to just the higher priority hazard identified via the risk characterization process.

Higher Priority Microbial Hazards

- Non-Typhi *Salmonella* spp. (raw and RTE product)
- *Listeria monocytogenes* (RTE product)
- *Clostridium botulinum* and toxins (raw and RTE product)
- Enterohemophagic, shigatoxigenic, enterotoxigenic and enteropathogenic *E. coli* (raw product)
- Lower Priority Microbial Hazards (Raw and Ready-to-Eat product) *Vibrio spp***.**
- Toxins associated with cyanobacteria
- *Edwardsiella tarda*
- *Shigella dysenteriae*
- *Pleisiomonas shigelloides*
- *Salmonella* Serotype *typhi*
- Waterborne parasites
- Viruses

Potential Indicator Bacteria

- Generic *Escherichia coli* (raw product)
- Gas-forming anaerobic bacteria (RTE product)
- Other indicator bacteria for assessing sanitation (raw and RTE product)

2.1.1 Higher priority microbial hazards

These include foodborne pathogens historically linked to consumption of various freshwater fish products.

Salmonella is a potential microbial hazard for aquatic environments and, thus, may be a concern with respect to fish products. **Non-*typhi Salmonella*** are regarded as one of the higher priority hazards because the general burden of illness from this pathogen in the U.S. remains a concern. We also note that there is evidence that at least one outbreak of human salmonellosis may have been related to catfish consumption. Specifically CDC surmised that an outbreak of 10 cases of salmonellosis (*Salmonella hadar*) at a restaurant in 1991 may have been caused by catfish consumption (U.S. CDC, 1991).

Salmonella was reported in 21% of 153 aquaculture catfish[27] collected from aquaculture ponds and retail markets (Wyatt, 1979) and can be harbored within catfish for 30 days after exposure to high levels (Ward, 1989). McCaskey et al. (1998) found *Salmonella* on 2.3% of 220 fillets sampled from three processing plants. Heinitz et al. (2000) reported FDA *Salmonella* testing from imported (11,312 samples) and domestic (768) seafood samples tested from 1990 to 1998. They found that 10% of imported and 2.8% of domestic raw seafood was positive for *Salmonella*. For Fin Fish/Skin Fish in that study, the percent positive was 12.2% and 1.3% for imported and domestic, respectively. An examination of FDA seafood import refusal data from 1998-2004 identified *Salmonella* contamination to be the most frequent violation in catfish (41.91% of violation categories)(Buzby, 2009)(Table 1). The combination of data presented in the literature, along with outbreak data and FDA import refusal data shown in Table 1 below, suggest that the highest microbial hazard associated with catfish (of the order Siluriformes) may be *Salmonella*.

[27] As mentioned above, the term *catfish* is used here and elsewhere to be consistent with the original source.

Table 1. FDA Violation Codes for Catfish Refusals (1998-2004)

FDA Violation Code[a]	Frequency	Percent of Refusals	Cumulative Frequency	Cumulative Percent
FALSE	1	0.74	1	0.74
FALSECAT	4	2.94	5	3.68
FILTHY	18	13.24	23	16.91
IMPTRHACCP	1	0.74	24	17.65
INCONSPICU	2	1.47	26	19.12
INSANITARY	5	3.68	31	22.79
LABELING	2	1.47	33	24.26
LACKS FIRM	7	5.15	40	29.41
LACKS N/C	3	2.21	43	31.62
LIST INGRE	1	0.74	44	32.35
LISTERIA	3	2.21	47	34.56
MFR INSAN	2	1.47	49	36.03
NO ENGLISH	1	0.74	50	36.76
NO PROCESS	2	1.47	52	38.24
NUTRIT LBL	3	2.21	55	40.44
SALMONELLA	57	41.91	112	82.35
USUAL NAME	19	13.97	131	96.32
WRONG IDEN	5	3.68	136	100.00

[a] All capitalized terms are FDA shorthand code for import violations. List can be found at www.fda.gov/ora/oasis/ora_oasis.

Listeria monocytogenes is a potential hazard for certain RTE fish products. Because it is a common environmental and aquatic contaminant, its presence in raw fish may pose an indirect risk in the form of cross-contaminating RTE product (Fernandes et al., 1997). Because *L. monocytogenes* (Lm) often contaminates and grows in cold-smoked fish products, there are likely to be similar risks for cold-smoked, RTE catfish (of the order Siluriformes) products. Chou et al. (2006) identified Lm in 25 to 47% of raw catfish fillets at three U.S. processing plants. Some isolates were persistently found in processed fillets, suggesting either that the sanitation was inadequate or that these isolates originated from the natural habitats of the fish. McCaskey et al. (1998) found a prevalence of 5.9% Lm on raw catfish fillets. Chou et al. (2006) found that Lm was more commonly isolated from catfish in the winter with a prevalence rate of 51%, compared to 41% in the spring, 36.7% in the fall and 19% in the summer.

Clostridium botulinum is a toxin-forming bacterium capable of causing a rare but life-threatening illness. *C. botulinum* has been isolated from catfish at retail (Baker et al., 1990). While toxins A and B are the primary botulinum toxin types associated with meat and poultry products, products from aquatic environments have the potential for contamination by Toxin E-type *C. botulinum*. Unlike the A- and B-type strains, type-E *C. botulinum* can grow and develop neurotoxin during refrigerated storage and, given the serious nature of the illness, warrants special consideration for effective control measures.

Enterohemorrhagic, shigatoxigenic, enterotoxigenic and enteropathogenic *E. coli* are fecal contaminants that cause waterborne and foodborne gastroenteritis. A 2003 outbreak linked catfish and coleslaw consumption to 41 cases of Enterotoxigenic *E. coli* (ETEC) O169:H41-related illness (Beatty, 2004). In this case the outbreak may have been due to cross-contamination, however it remains clear that enterotoxigenic (ETEC) and enteropathogenic *E. coli* (EPEC) are recognized waterborne hazards that could be associated with raw fish. Shigatoxigenic (STEC) and Enterohemorrhagic (EHEC) *E. coli*, including *E. coli* Serotype O157:H7, have been associated with both waterborne and foodborne gastroenteritis outbreaks. Runoff from ruminant animal farms is a common source for waterborne *E. coli* O157:H7 contamination; proximity to animal farms or access of wild animals to aquaculture ponds could be significant contributing factors.

2.1.2 Lower Priority Microbial Hazards

These include a broad scope of recognized waterborne pathogens, both within and beyond the U.S., that could be harbored on raw fish products, however, the potential for catfish (of the order Siluriformes) as a vector for foodborne illness remains unclear. This list includes:

***Vibrio* spp.** These known aquatic pathogens include *V. parahaemolyticus* and *V. vulnificus*, associated with seafood products from saltwater and brackish water sources. Their potential for association with Siluriformes from freshwater environments is unclear. Although most environmental *V. cholerae* isolates do not produce cholera toxin, Fernandes et al. (1997) found *V. cholerae* in 10-45% of catfish fillets tested. Catfish (of the order Siluriformes) consumption has been associated, though not definitively implicated, in *Vibrio* illness in immunocompromised people.

Toxins associated with cyanobacteria (i.e., blue-green algae). These can be hepatotoxic and neurotoxic for humans. Contamination is typically associated with off flavor, so acute exposure has been rare. It is not clear whether there could be more subtle public health risks for exposure to lower levels of these toxins.

Edwardsiella tarda. This is a catfish (of the order Siluriformes) pathogen that can also cause gastrointestinal illness in immunocompromised people, though human illness has not been definitively linked to Siluriformes consumption.

Shigella dysenteriae. This is a common cause of waterborne gastroenteritis in the developing world, and has the potential to contaminate fish and other food products.

Plesiomonas shigelloides. This has been isolated from freshwater fish in tropical climates. *P. shigelloides* strains associated with human gastrointestinal disease have been isolated from patients living in tropical and subtropical areas. Such infections are rarely reported in the U.S. or Europe.

Salmonella* serotype *typhi. This has not been a focus of FSIS testing because it is typically associated with human rather than food animal carriage; in fact, it has not been grouped with other *Salmonella* species in this assessment because it is not readily detected by the current FSIS *Salmonella* testing method. However, it is a known agent for waterborne gastroenteritis, so it might be possible that Siluriformes are vectors for typhoid fever.

Waterborne parasites. Organisms with potential to contaminate domestic and/or imported fish include *Taenia solium*, *Giardia lamblia*, *Enterobius*, *Cryptosporidium*, *Gnathostoma spinigerum*, *Opisthorchis viverrini* and others.

Viruses (e.g., rotavirus). These can be associated with aquatic environments, but the potential for Siluriformes as a vector for foodborne illness remains unclear.

Other potential pathogens have been tied to Siluriformes and aquatic farm environments, but illness associations with Siluriformes handling or consumption remain unclear. These pathogens include *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, two opportunistic human pathogens that are typically not associated with either foodborne or waterborne illness, and *Aeromonas hydrophila*, a bacterium that has been considered a suspect but unsubstantiated pathogen.

2.1.3 Potential Indicator Bacteria

Potential indicator bacteria include organisms that could be used to indicate the presence of fecal contamination or insanitary conditions, and include:

Generic *Escherichia coli*. These may be useful for understanding the relative risk of aquatic farm environments and raw products. Generic *E. coli* is associated with fecal contamination and is a commonly used indicator organism for sanitation in the food-processing environment. The International Commission on Microbiological Specifications for Foods recommends that good-quality fresh or frozen fish contain less than 11 CFU *E. coli* per gram (ICMSF, 1986). McCaskey et al. (1998) isolated 2.2 log CFU *E. coli* per gram from catfish fillets. Ramos and Lyon (2000) reported levels of -0.8/0 log CFU/g *E. coli* for whole catfish and catfish fillets, respectively. The Sea Grant Extension Program and the International Commission on Microbiological Specifications for Foods recommends *E. coli* limits of 1 and 2.7 log CFU/g for good quality and marginally acceptable fresh and frozen fish products, respectively (ICMSF, 1986).

Gas-forming anaerobic bacteria. Testing could be applied as indicators of potential *C. botulinum* and related proteolytic *Clostridium* spp.

Other indicator bacteria for consideration in assessing sanitation on raw and RTE catfish (of the order Siluriformes). These could include aerobic plate count (APC), psychrotrophs, coliforms, Enterobacteriaceae, and enterococci. Farid et al. (2000) found levels of 4.3, 2.9 and 2.9 log CFU/g for APC, psychrotrophs and coliforms, respectively. Ramos and Lyon (2000) reported levels of 6.9/7.4 log CFU/g for APC, 6.11/7.11 log CFU/g for anaerobic plate count, and 2.41/2.73 log CFU/g for coliforms for whole catfish and catfish fillets samples respectively. Andrews et al. (1977) observed APC ranging from 3.8 to 8.3 log CFU/g, total coliforms from <0.48 to 3.97 log CFU/g in fresh catfish samples. The Sea Grant Extension Program and the International Commission on Microbiological Specifications for Foods recommends that fresh or frozen fish contain less than 5.7 log CFU/g APC for good quality products and less than 7.0 log CFU/g APC for marginally acceptable products.

2.1.4 Literature Summary: Chemical Hazards

McCaskey et al. (1998) suggest that, in general, catfish consumption is considered to pose a relatively low risk to consumers from a microbiological perspective. The author speculates that this may be "because their incidence on catfish is low and because catfish are well cooked prior to being consumed".

The CDC reports that fish and shellfish account for 5% of the individual cases and 10% of all foodborne illness outbreaks, with most of these resulting from consumption of raw molluscan shellfish. Food poisoning microorganisms associated with fish include bacteria indigenous to water, those associated with pollution of aquatic environments, and those introduced to animals and their products during post harvest handling and processing (Flick, 2008).

2.2 Identification of Potential Chemical Hazards

Consideration of the likelihood of contamination for catfish (of the order Siluriformes) must include the conditions under which the fish are raised, transported, and processed. As such, the potential impacts of environmental factors, aquaculture and processing practices on the exposure of hazards to consumers are considered here.

The information obtained about potential hazards is based on current Siluriformes aquaculture practices. It was gathered through discussions with representatives from multiple federal agencies, academic institutions, industry representatives and non-government organizations. Information was also obtained through numerous literature searches in PubMed, Food Science and Technology Abstracts, Chemical Abstracts, USDA DigiTop and Web of Science databases.[28] The key words used during chemical oriented-database searches included, but were not limited to "catfish" in combination with one or more of the following: "hazard", "food safety", "food borne", "retail", "process*", "human", "chemical", "pesticide", "organo*", "polychlorinated", "dioxin", "herbicide", "veterinar*" and "drug". The United States Department of Agriculture, United States Environmental Protection Agency (EPA), the FDA, and the Centers for Disease Control and Prevention (CDC) websites were also used to identify the statistics and regulations to analyze in the hazard identification process.

This approach led to the identification of several hazards that might be associated with catfish (of the order Siluriformes). Potential chemical hazards included veterinary drugs used in aquaculture as well as pesticides and heavy metals likely to be present in the environment in and/or around fish farms and processing facilities. Some chemicals are used in multiple ways and may therefore appear in more than one of the following lists, including drugs, pesticides, and other chemicals associated with aquaculture.

2.2.1 Drugs

The following is an alphabetical list of drugs that were identified to be linked with aquaculture generally. The focus is on domestic drugs due to available information from the FDA website (www.FDA.gov). At the end of this section is a list of some of the drugs used in foreign aquaculture.

FDA has a drug residue monitoring program that includes Chloramphenicol, Nitrofurans, and Fluoroquinolones, Malachite green (and its metabolite Leucomalachite green), Crystal (Gentian) violet (and its metabolite Leucogentian violet), Quinolones (Oxolinic acid and Flumequine), Ivermectin, Methyltestosterone and oxytetracycline (U.S. FDA, 2008a).

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[28]PubMed: http://www.ncbi.nlm.nih.gov/pubmed/;
Food Science and Technology Abstracts: http://www.foodsciencecentral.com/;
Chemical abstracts: http://pubs.acs.org/;
USDA DigiTop: http://riley.nal.usda.gov/digitop_interim/proxy_stop403.html;
Web of Science: http://www.isiwebofknowledge.com. These websites were accessed between July 2008 and November 2009.

Acetic acid

This is an FDA low regulatory priority aquaculture drug. The allowed use is as a parasiticide for fish at a dose of 1,000 to 2,000 ppm dip for 1 to 10 minutes. There is no withdrawal time or regulatory residue level.

Calcium chloride

This is an FDA low regulatory priority aquaculture drug. The allowed use is to increase water calcium concentration to ensure proper egg hardening. Dosages used would be those necessary to raise calcium concentrations to 10-20 ppm. This drug can also be used up to 150 ppm indefinitely to increase the hardness of water during the holding and transport of fish to enable the maintenance of osmotic balance. There is no withdrawal time or regulatory residue level.

Calcium oxide

This is an FDA low regulatory priority aquaculture drug. The allowed use is as an external protozoacide for fingerlings to adult fish at a concentration of 2000 mg/L for 5 seconds. There is no withdrawal time or regulatory residue level.

Carbon dioxide gas

This is an FDA low regulatory priority aquaculture drug. The allowed use is as an anesthetic in cold, cool and warm water fish. There is no withdrawal time or regulatory residue level.

Chorionic Gonadotropin

This hormone drug (Chorulon) is FDA approved as an intramuscular injection for the use in brood fish to aid in spawning. The approved dosage is 50-510 IU/lb for male fish and 67-1816 IU/lb for female fish. It has been approved for up to 3 doses, not to exceed 25,000IU in fish intended for human consumption and is restricted to use by a licensed veterinarian. There is no withdrawal time or regulatory residue level.

Clove Oil

This substance is not an approved drug by the FDA for the use in aquaculture. Clove Oil is an anesthetic when used as an immersion for fish. There is some concern about anesthetic use in the transport of fish from the farm to the processing plant. According to the FDA Guidance for Industry #150 'Concerns Related to the use of Clove Oil as an Anesthetic for Fish' (April 2007), even though clove oil and its components are generally recognized as safe (GRAS) for use in dental cement and as a food additive, it is not GRAS for use as an anesthetic for fish (U.S. FDA, 2007). Clove oil is made up of 85-95% eugenol and the rest consists of isoeugenol and methyleugenol. These ingredients have been tested by the National Toxicology Program. The results for carcinogencity for isoeugenol and eugenol were equivocal carcinogen, methyleugenol was carcinogenic to rodents.

Copper sulfate

FDA has deferred regulatory action on copper sulfate pending further study. It can be used under the Investigational New Animal Drugs (INAD). Such products can be used in accordance with the EPA registered label. There is no withdrawal time or regulatory residue level.

Florfenicol

This drug is FDA approved as an antibiotic feed additive for the control of catfish enteric septicemia caused by *Edwardsiella ictaluri and* columnaris associated with Flavobacterium columnare. The approved dosage is 10mg/kg/day for 10 consecutive days. It has a withdrawal time of 12 days, a tolerance level of 1 ppm.

Formalin

This drug is FDA approved as in immersion for the control of external protozoa and monogenetic trematodes on fish and fungi on eggs. The approved dosage for parasite control on adults in tanks and raceways is 250 IU/L indefinitely. For fungi control on eggs the approved dosage is 1000-2000ppm for 15 minutes. There is no withdrawal time or regulatory residue level.

Fuller’s earth

This is an FDA low regulatory priority aquaculture drug. The allowed use is to reduce the adhesiveness of fish eggs to improve hatchability. There is no withdrawal time or regulatory residue level.

Garlic (whole form)

FDA classifies garlic as an aquaculture drug and categorizes it as low regulatory priority. The allowed use is for the control of helminthes and sea lice infestations of marine salmonids at all life stages. There is no withdrawal time or regulatory residue level.

Hydrogen Peroxide

Hydrogen peroxide is classified as a drug for aquaculture by FDA and approved as an immersion for the control of columnaris disease caused by *Flavobacterium columnare (Flexibacter columnaris)* and for the control of *saprolegniasis* fungi on eggs. The approved dosage for fungi control on eggs in warm water it is 750-1000mg/L for 15 minutes. For the treatment of columnaris disease the approved dosage is 100mg/L for 30 minutes or 50-100 mg/L for 60 minutes once per day, every other day for 3 treatments. There is no withdrawal time or regulatory residue level.

Ice

FDA classifies ice as an aquaculture drug and categorizes it as low regulatory priority. The allowed use is to reduce metabolic rate of fish during transport. There is no withdrawal time or regulatory residue level.

Magnesium sulfate

This is an FDA low regulatory priority aquaculture drug. The allowed use is to treat external monogenic trematode infestations and external crustacean infestations in fish at all life stages. It is used in all freshwater species. The allowed dose is an immersion at 30,000 mg $MgSO_4$/L and 7000 mg NaCl/L solution for 5 to 10 minutes. There is no withdrawal time or regulatory residue level.

Onion (whole form)

FDA classifies whole onions as an aquaculture drug and categorizes it as low regulatory priority. The allowed use is to treat external crustacean parasites and to deter sea lice from infesting the external surfaces of salmonids at all life stages. There is no withdrawal time or regulatory residue level.

Oxytetracycline dihydrate (Terramycin)

Terramycin 200 is FDA approved as a medicated feed for the control of Pseudomonas disease caused by *Pseudomonas* and bacterial hemorrhagic septicemia caused by *Aeromonas liquefaciens*. The approved dosage is 2.5-3.75g/100lb/day for 10 days. It has a withdrawal time of 21 days and a tolerance level of 2ppm.

Oxytetracycline HCl (Terramycin)

This drug is FDA approved as an immersion for the use with mark skeletal tissues. The approved dosage is 200-700mg/L for 2-6 hours. It has no withdrawal times and a tolerance level of 2ppm.

Papain

Papain is an FDA low regulatory priority aquaculture drug. The allowed use is as a 0.2% solution in removing the gelatinous matrix of fish egg masses in order to improve hatchability and decrease the incidence of disease. There is no withdrawal time or regulatory residue level.

Potassium chloride

Potassium chloride is an FDA low regulatory priority aquaculture drug. The allowed use is as an aid in osmoregulation which helps to relieve stress and prevent shock. Allowed dosages are those that would be necessary to increase chloride ion concentration to 10-2000 mg/L. There is no withdrawal time or regulatory residue level.

Potassium permanganate

FDA has deferred regulatory action on potassium permanganate pending further study. It can be used under the Investigational New Animal Drugs (INAD). Such products can be used in accordance with the EPA registered label. There is no withdrawal time or regulatory residue level.

Povidone iodine

Povidone iodine is an FDA low regulatory priority aquaculture drug. The allowed use is as an egg surface disinfectant during and after water hardening at a dose of 100 ppm solution for 10 minutes. There is no withdrawal time or regulatory residue level.

Sodium bicarbonate

FDA classifies sodium bicarbonate as an aquaculture drug and categorizes it as low regulatory priority. The allowed use is as a means of introducing carbon dioxide into the water to anesthetize fish at a dose of 142-642 ppm for 5 minutes. There is no withdrawal time or regulatory residue level.

Sodium chloride

FDA classifies sodium chloride (salt) as an aquaculture drug and categorizes it as low regulatory priority. The allowed use is as an osmoregulatory aid for the relief of stress and prevention of shock at a dose of 0.5% to 1.0% solution for an indefinite period. Another allowed use is as a parasiticide at a dose of 3% solution for 10 to 30 minutes. There is no withdrawal time or regulatory residue level.

Sodium sulfite

Sodium sulfite is an FDA low regulatory priority aquaculture drug. The allowed use is as a 15% solution for 5 to 8 minutes to treat eggs in order to improve their hatchability. There is no withdrawal time or regulatory residue level.

Sulfadimethoxine, ormetoprim

Sufadimethoxine is FDA approved as an antibiotic feed additive for the control of enteric septicemia caused by *Edwardsiella ictaluri*. The approved dosage is 50mg/kg/day for 5 days. It has a withdrawal time of 3 days and a tolerance level of 0.1ppm.

<u>Thiamine hydrochloride</u>

Thiamine hydrochloride is an FDA low regulatory priority aquaculture drug. The allowed use is to prevent or treat thiamine deficiency in salmonids. The allowed dose is to immerse the eggs in a solution of up to 100 ppm for up to 4 hours during water hardening. Sac fry are allowed to be immersed in a solution of up to 1,000 ppm for up to 1 hour. There is no withdrawal time or regulatory residue level.

<u>Tricaine methanesulfonate (MS-222)</u>

Tricaine methanesufonate is FDA approved as an immersion for the temporary immobilization of fish. The approved dosage is 15-330mg/L and its use in fish intended for food is restricted to Ictaluidae, Salmonidae, Esocidae and Percidae. It has a withdrawal time of 21 days with no regulatory residue level.

<u>Urea and Tannic acid</u>

Urea and tannic acid are FDA low regulatory priority aquaculture drugs. The allowed use is to denature the adhesive component of fish eggs at concentrations of 15 g urea and 20 g NaCl per 5 liters of water for about 6 minutes, followed by a separate solution of 0.75 g tannic acid per 5 liters of water for an additional 6 minutes. This dose should treat about 400,000 eggs. There is no withdrawal time or regulatory residue level.

Box 2.1 contains a non-inclusive list of drugs used in foreign aquaculture. These drugs are currently not approved for use in aquaculture by the FDA.

Box 2.1 Non-inclusive List of Drug Used in Foreign Agriculture [29]

Azamethiphos	Josamycin	Praziquantel
Chloramphenicol	Kanamycin	Rifampicin
Dichlorovos	Levamisole	Saponin
Diflubenzuron	Malachite green	Sarafloxacin
Enrofloxacin	Methyltestosterone	Spiramycin
Eugenol	Nalidixic Acid	Streptomycin
Fenthion	Nifurpirinol	Teflubenzuron
Flumequine	Nitrofuran	Testosterone
Furazolidone	Nitrofurantoin	Thiamphenicol
Glucans	Nitrofurazone	Tributyltin
Isoeugenol	Norfloxacin	Trichlorfon
Ivermectin	Oxolinic Acid	Trifluralin

<u>Drugs prohibited under the Animal Medicinal Drug Use Clarification Act</u>

The Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 (21 CFR 530) allows veterinarians to use approved FDA drugs outside of the labeled species, indication, dose, frequency or route of administration so long as a valid veterinarian-client-patient relationship exists. This is called extra-label use. The following drugs are prohibited from extra-label use in food animals (21 CFR Part 530.41).

- Chloramphenicol- broad spectrum antibiotic known to cause aplastic anemia in humans (U.S. FDA, 1992; Young, 2002)
- Clenbuterol- β2 adrenergic agonist used as a growth enhancer and linked with acute poisoning of humans who consumed meat from animals given clenbuterol (U.S. FDA, 1991; Chan, 1999)
- Diethylstilbestrol – synthetic nonsteroidal estrogen and a teratogen when given to pregnant women (U.S. FDA, 1999)

[29] This list was generated with help from Dr. Fran Pell at the Center for Veterinary Medicine, Food and Drug Administration (U.S. FDA, 2008b).

- Dimetridazole – a nitroimidazole
- Ipronidazole - a nitroimidazole
- Other nitroimidazoles – antibiotic with mutagenic concerns (U.S. FDA, 2009)
- Furazolidone – antibiotic and anti-protozoal whose residues in edible tissues are known carcinogens (U.S. FDA, 2002a)
- Nitrofurazone – a nitrofuran antibiotic whose residues in edible tissues are known carcinogens (U.S. FDA, 2002a)
- Fluoroquinolones – broad spectrum antibiotic with toxicological concerns (U.S. FDA, 2002b)
- Glycopeptides – antibiotics banned from extra-label use due to toxicological concern (U.S. FDA, 1997)
- Sulfonamides – antibiotic banned from off label use in lactating dairy cattle; sulfonamide use in humans can cause severe allergic reactions to those allergic
- Phenylbutazone – non-steroidal anti-inflammatory (NSAID) banned from off label use in female dairy cattle over 20 months of age; can cause blood dyscrasias, hypersensitivity reactions and is carcinogen in humans (U.S. FDA, 2003)

2.2.2 Pesticides

The section contains an alphabetical list of pesticides that were identified to be linked with aquaculture and a brief description of some toxic endpoints that have been associated with those chemical. It is important to note, however, that some of the data on toxicity comes from animal studies and often with very high doses. This list was generated from the FDA/CFSAN Fish and Fisheries Products and Controls Guidance, third edition June 2001 (U.S. FDA/CFSAN, 2001); the *Guide to Drug, Vaccine, and Pesticide Use in Aquaculture*, April 2007 revision issued by the Federal Joint Subcommittee on Aquaculture working group on quality assurance in aquaculture production (US Federal Joint Committee on Aquaculture, 2007). Tolerances are included when available. Information on toxicity was found using the U.S. EPA Integrated Risk Information System (IRIS) (U.S. EPA, 2009) and other sources when noted.

2, 4-Dichlorophenoxyacetic acid (2, 4-D)

2,4-D (Chemical Abstracts Service Registry Number (CASRN) 94-75-7) is one of a family of herbicides known as the chlorophenoxy herbicides. Hematologic, hepatic and renal toxicity has been seen in rats orally exposed to 2,4-D. EPA established an oral reference dose (RfD[30]) for 2,4-D of 0.01 mg/kg/day using that study; the RfD includes a 100-fold uncertainty factor. The FDA/CFSAN Fish and Fisheries Products and Control Guidance set a tolerance level for 2, 4-D at 0.1 ppm.

Acetic Acid

Acetic acid (CASRN 64-19-70) is an EPA registered aquatic herbicide. It is the main ingredient in vinegar apart from water. The EPA has not developed an RfD for acetic acid. Much of its toxic effects are related its caustic properties if at a high-enough concentration,

Aldrin/Dieldrin

U.S. production of the organochlorine pesticicides aldrin and dieldrin was discontinued in 1989, but they take decades to break down in the environment and they can bioaccumulate in fish. In 1988 EPA has set an RfD for aldrin (CASRN 309-00-2) of $3x10^{-5}$ mg/kg/day that includes a 1,000-fold uncertainty factor, and for dieldrin (CASRN 60-57-1) of $5x10^{-5}$ mg/kg/day; the RfD includes a 100-fold uncertainty factor. EPA classifies both as class B2 probable human carcinogens. The Agency of Toxic Substances & Disease Registry, however, indicates that "current mechanistic data suggest that the mouse carcinogenicity data may not be highly relevant to humans" (ATSDR, 2002). The FDA/CFSAN Fish and Fisheries Products and Control Guidance lists an action level for Aldrin/Dieldrin at 0.3 ppm.

[30] EPA's reference dose (RfD) is "[a]n estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments."
(Available at: http://www.epa.gov/risk_assessment/glossary.htm#r; accessed July 31, 2014)

Ammonia

EPA has not established an RfD for amonia (CASRN 7664-41-7), but ATSDR "cites irritative and corrosive properties" from excessive exposures as a main concern and does not consider oral exposure to be an exposure route of concern (ATSDR 2004).

Antimycin A

Antimycin A (CASRN 1397-94-0) is an EPA registered fish toxicant. In a 2007 Reregistration Eligibility Decision document, EPA (2007) determined that there is insufficient data for conducting a risk assessment, and EPA has not developed an IRIS profile for this chemical. It is considered a Restricted Use Pesticide (RUP) and, therefore, each application must be approved by appropriate state and federal fish and wildlife agencies and there are requirements for not harvesting fish that survived a selective kill with antimycin A for 12 months.

Benzenepropanoic acid (Phenylpropanoic acid)

Benzenepropanoic acid (CASRN 501-52-0) is an EPA registered aquatic herbicide. The EPA does not have information for benzenepropanoic acid available on IRIS.

Bleach (Calcium Hypochlorite, Sodium Hypochlorite)

Calcium hypchlorite (CASRN 7778-54-3) and sodium hypochlorite (CASRN 7681-52-9) are chlorinated inorganic disinfectants commonly referred to as bleach. In an RED in 1991, EPA concluded that "the risks from chronic and subchronic exposure to low levels of these pesticides are minimal and without consequence to human health."

Butoxyethyl 2,4-dichlorophenyoxyacetate

Butoxyethyl 2,4-dichlorophenyoxyacetate (1929-73-3) is the butoxyethyl ester form of 2,4-D and is an EPA registered chlorophenoxy aquatic herbicide. The potential toxicity of 2,4-D is discussed above.

Chlordane

Although the EPA cancelled the use of chlordane (CASRN 12789-03-6) as a pesticide in 1988, residues could still persist in soil and the chemical is capable of bioaccumulating in both marine and freshwater species. EPA has established an RfD of $5x10^{-4}$ mg/kg/day for chlordane on the basis of an oral study in mice; the RfD includes a 300-fold uncertainty factor. The potential adverse effects of high dose of this chemical include hepatic necrosis. Chlordane is classified as a class B2 probable human carcinogen. The FDA/CFSAN Fish and Fisheries Products and Control Guidance lists an action level for Chlordane at 0.3 ppm.

Chlordecone

Chlordecone (CASRN 143-50-0) is no longer made or used in the United States. All U.S. product registrations were cancelled by EPA by 1978 and it revoked all residue tolerances in or on raw agricultural products within its purview. Chlordene has the ability to bioaccumulate in fish. EPA has established an RfD of $3x10^{-4}$ mg/kg/day for chlordecone on the basis of a rat feeding study showing renal lesions; the RfD includes an uncertainty factor of 300. The FDA/CFSAN Fish and Fisheries Products and Control Guidance lists an action level for Chlordecone at 0.3 ppm. Chlordecone is listed as likely to be carcinogenic to humans and has an oral slope factor of 10 mg/kg/day.

Chlorine

Chlorine (CASRN 7782-50-5) is an EPA registered algaecide. EPA has established an RfD of 0.1 mg/kg/day on the basis of a chronic drinking water study in rats and a 100-fold uncertainty factor from the no-observed-adverse-effect-level (NOAEL); no adverse effects were seen at the highest dose used in the study.

Chlorophenoxy compounds

Chlophenoxy compounds refers to a family of herbicides. The toxicity of the relevant members of this family are discussed under the specific chemical.

Copper Compounds

A number of copper compounds are registered by EPA as algaecides and aquatic herbicides, including: copper carbonate (CASRN 12069-69-1), copper ethanolamine complex (CASRN 14215-52-2), copper hydroxide (20427-59-2), copper sulfate (1344-73-6) and copper triethanolamine complex (82027-59-6). The EPA has not established an RfD for copper compounds, but states that a risk assessment conducted as part of a 2009 Revised Eligibility Decision for copper compounds indicates "that there are no residential, dietary, occupational, or aggregate risks of concern resulting from the use of copper pesticides" (EPA, 2010) (EPA EPA-HQ-OPP-2010-0212; Coppers Summary Document Registration Review: Initial Docket September 2010; .

Crystal Violet

FDA has designated crystal violet (also known as Gentian violet; CASNR 548-62-9) as an unapproved antifungal agent. Crystal violet is absorbed into fish tissue and is reduced metabolically to leucocrystal violet. Crystal violet is mutagenic, and chronic studies in mice demonstrate carcinogenicity. The EPA does not have information for crystal violet available on IRIS.

DDT (p,p'-Dichlorodiphenyltrichloroethane), TDE, DDE (p,p'-Dichlorodiphenyldichloroethylene)

DDT (CASRN 50-29-3) has not been permitted in the U.S. since 1972 except in cases of public emergency, but it is still used elsewhere in the world for the control of malaria. This pesticide has the ability to bioaccumulate in fish. The FDA/CFSAN Fish and Fisheries Products and Control Guidance lists an action level for DDT, TDE, DDE at 5 ppm. EPA has established an RfD of $5x10^{-4}$ mg/kg/day which is based on liver lesions; the RfD includes a 100-fold uncertainty factor. DDT and DDE (72-55-9) are classified as a class B2 probable human carcinogen under. The EPA does not have information for TDE available on IRIS.

Diflubenzuron

Diflubenzuron (CASRN 35367-38-5) is an EPA registered invertebrate toxicant. EPA has established an RfD of 0.02 mg/kg/day on the basis of methemoglobin and sulfhemoglobin formation; the RfD includes a 100-fold uncertainty factor.

Dimethylamine salt of 2,4-D

The dimethylamine salt of 2,4-D (CASRN 2008-39-1) is an EPA registered chlorophenoxy aquatic herbicide. The EPA does not have information for dimethylamine available on IRIS.

Diquat (Diquat Dibromide)

Diquat (CASRN 85-00-7) is an EPA registered algaecide and aquatic herbicide. The FDA/CFSAN Fish and Fisheries Products and Control Guidance lists a tolerance level for Diquat at 0.1 ppm. The EPA has established an RfD of 2.2×10^{-3} mg/kg/day on the basis of a study in rats showing minimal lens opacity and cataracts; the RfD includes a 100-fold uncertainty factor. EPA does not have a carcinogenicity assessment for diquat.

Endothall

Endothall (CASRN 145-73-3) is an EPA registered algaecide and aquatic herbicide. The EPA has set a tolerance in fish at 0.1ppm for Endothall residues. The EPA has has established an RfD of 0.02 mg/kg/day on the basis of a study in dogs showing increased absolute and relative weights of stomach small intestine; the RfD includes a 100-fold uncertainty factor. EPA does not include a carcinogenicity assessment of endothall.

Endrin

Endrin (CASRN 72-20-8) is an organochlorine pesticide banned by EPA because of its persistence in the environment. The EPA has established an RfD of 3×10^{-4} mg/kg/day on the basis of a study in dogs showing mild histological lesions in liver and occasional convulsions; the RfD includes a 100-fold uncertainty factor. Endrin is classified as class D, not classifiable as to carcinogenicity for humans.

Fluridone (Ansi)

Fluridone (CASRN 59756-60-4) is an EPA registered aquatic herbicide. The FDA/CFSAN Fish and Fisheries Products and Controls Guidance lists a tolerance level for Fluridone at 0.5 ppm. The EPA has an RfD of 0.08 mg/kg/day on the basis of a rat study glomerulonephritis, atrophic testes, eye keratitis along with a decrease in body and organ weights; the RfD includes a 100-fold uncertainty factor.

Glyphosate Isopropylamine Salt (Glyphosate)

Glyphosate (1071-83-6) is an EPA registered aquatic herbicide. The FDA/CFSAN Fish and Fisheries Products and Controls Guidance lists a tolerance level for Glyphosate at 0.25 ppm. The EPA has an RfD of 0.1 mg/kg/day for glyphosate on the basis of a 3-generational rat study showing kidney defects in subsequent generations; the RfD includes a 100-fold uncertainty factor. Glyphosate is classified as class D, not classifiable as a human carcinogen.

Heptachlor/Heptachlor Epoxide

Heptachlor (CASRN 76-44-8) and heptachlor epoxide (1024-57-3) have not been used since 1988, but are still registered by the EPA for killing fire ants in buried power transformers. They have the ability to bioaccumulate in fish. The FDA/CFSAN Fish and Fisheries Products and Controls Guidance lists an action level for both chemicals at 0.3 ppm. The EPA has an RfD for heptachlor of $5x10^{-4}$ mg/kg/day on the basis of a study in rats showing increased liver weight; the RfD for heptachlor includes a 300-fold uncertainty factor. The RfD for heptachlor epoxide is $1.3x10^{-5}$ mg/kg/day on the basis of a study in dogs showing an increased liver-to-body ration in both males and females; the RfD for heptachlor epoxide includes a 300-fold uncertainty factor. EPA classifies both heptachlor and heptachlor epoxide as class B2, probable human carcinogen.

Hexachlorobenzene

The pesticide hexachlorobenzene (CASRN 118-74-1) is banned by the EPA. The EPA has established an RfD of $8x10^{-4}$ mg/kg/day on the basis of findings of liver effects in a chronic rat study; the RfD includes a 100-fold uncertainty factor. EPA classifies hexachlorobenzene as a class B2, probable human carcinogen.

Imazapyr (isopropylamine salt)

Imazapyr (CASRN 81334-34-1) is an EPA registered aquatic herbicide. The EPA does not have information for Imazapyr available on IRIS.

Lime (calcium/magnesium hydroxide)

Lime (calcium hydroxide, CASRN 1305-62-0; magnesium hydroxide, 1309-42-8) is used to improve pond water quality. It is considered low toxicity.

Lindane (gamma-hexachlorocyclohexane)

Lindane (CASRN 58-89-9) is a pesticide for which EPA has established an RfD of $3x10^{-4}$ mg/kg/day on the basis of liver and kidney toxicity in a rat oral bioassay; the RfD has includes a 1000-fold uncertainty factor. EPA indicates that there is no data for conducting a carcinogenicity assessment for lindane.

Malachite Green and Leucomalachite Green

Malachite green (CASRN 569-64-2) and leucomalachite green (CASRN 129-73-7) are fungicides that are prohibited by FDA and are not registered for use with EPA. Malachite green is excreted rapidly but >80% is metabolized into leucomalachite green which can remain in the muscle for months. A National Toxicology Program (NTP) feed studies of these compounds in rats and mice found equivocal evidence of carcinogenic activity in some species. Nonneoplastic lesions were also seen in the thyroid gland and liver. This hazard is considered a mutagen and teratogen. Brilliant Green is another compound similar in structure to Malachite Green and should also be considered a hazard.

Mirex

The use of the pesticide mirex (CASRN 2385-85-5) was cancelled in the U.S. between 1977-1978. It has the ability to bioaccumulate in fish. The FDA/CFSAN Fish and Fisheries Products and Controls Guidance lists an action level for Mirex at 0.1 ppm. The

EPA has established an RfD of $2x10^{-4}$ mg/kg/day on the basis of liver cytomegaly, fatty metamorphosis, angiectasis and thyroid cystic follicles in a chronic rat feeding study; the RfD includes a 300-fold uncertainty factor. EPA indicates that there is no data for conducting a carcinogenicity assessment for mirex.

Rotenone (Cube Resins Other than Rotenone) (Piperonyl Butoxide Technical)

Rotenone (CASRN 83-79-4) is an EPA registered fish toxicant that is a Restricted Use Pesticide (RUP). Each application, therefore, must be approved by appropriate state and federal fish and wildlife agencies. The EPA has established an oral RfD of $4x10^{-3}$ mg/kg/day for rotenone on the basis of a 2-generation rat study showing reduced pup weight; the RfD includes a 100-fold uncertainty factor. EPA indicates that there is no data for conducting a carcinogenicity assessment for rotenone.

Simazine

The FDA/CFSAN Fish and Fisheries Products and Controls Guidance lists a tolerance level for Simazine (CASRN 122-34-9) at 12 ppm. EPA has established an oral RfD of $5x10^{-3}$ mg/kg/day on the basis of a reduction in weight gain and hematological changes in females in a 2-year rat study; the RfD includes a 100-fold uncertainty factor. EPA indicates that there is no data for conducting a carcinogenicity assessment for simazine.

Sodium 2,4-dichlorophenoxyacetate (2,4-D, sodium salt)

Sodium 2,4-D is the sodium salt of 2,4-D and is an EPA registered chlorophenoxy aquatic herbicide. The potential toxicity of 2,4-D is discussed above.

Sodium Bromide

EPA re-registered the algaecide sodium bromide (CASRN 7647-15-6) in 1993. At that time it concluded that the use of "products containing sodium bromide and sodium chloride as labeled and specified in the [Reregistration Eligibility Decision] will not pose unreasonable risks or adverse effects to humans."

Sodium Percarbonate

Sodium percarbonate (sodium carbonate peroxyhydrate; CASRN 15630-89-4) dissolves into hydrogen peroxide, carbonate and sodium. It acts as an oxidizing agent commonly used in cleaning products, and is registered with EPA as an algaecide and fungicide. This is an EPA registered algaecide. EPA determined the risks to humans from sodium percarbonate use are very low.

Tartrazine/Erioglaucine

Tartrazine (1934-21-0) and erioglaucine (3844-45-9) are EPA registered algaecides and aquatic herbicides. In a 2005 RED, EPA concludes that "erioglaucine and tartrazine both have very low toxicity potentials."

Tea seed oil and mahua oil cake (sapogenin glycosides)

Tea seed oil is an edible oil made by pressing the seeds of the camellia trees. Mahua oil cake is also an edible oil.

Triazine Herbicides

The family of triazine herbicides includes atrazine (CASRN 1912-24-9) and propazine (139-40-2). EPA has established an RfD for atrazine of 0.035 mg/kg/day on the basis of a 2-year rat study showing a reduction in weight gain; the RfD includes a 100-fold uncertainty factor. EPA has established an RfD for propazine RfD of 0.02 mg/kg/day in a 2-year rat feeding study; the RfD includes a 300-fold uncertainty factor. EPA indicates that there is no data for conducting a carcinogenicity assessment for atrazine or propazine.

2.2.3 Other Chemicals Associated with Aquaculture

The following is an alphabetical list of other chemicals that were identified to be linked with aquaculture. This list was generated from WHO technical report series 883, Food Safety Issues Associated with Products from Aquaculture from FAO/NACA/WHO, 1999 (WHO/FAO/NACA, 1999).

Agricultural limestone

Water treatment used to raise pH and to sterilize pond soils between production cycles. FDA lists ground limestone as a GRAS food additive.

Aluminum Sulfate

Aluminum sulfate (CASRN 10043-01-3) is a flocculant used to cause suspended clay particles to precipitate to clear water turbidity. EPA has set a non-enforceable secondary drinking water quality standard for aluminum for aesthetics (odor, taste or color) not health (0.05–0.2 mg/L) and FDA has established an allowable level for bottled water (0.2 mg/L). FDA lists aluminum sulfate as a food and animal feed additive.

Ammonium phosphate (mono- and dibasic)/Ammonium Sulfate/Ammonium Nitrate

Ammonium phosphate (CASRN 10361-65-6), ammonium sulfate (CASRN 7783-20-2), and ammonium nitrate (6484-52-2) are fertilizers for phytoplankton. The main toxic concerns those chemicals are acute effects from spills or accidents. FDA lists ammonium phosphate and sulfate as food additives.

Benzalkonium chloride (alkyldimethylbenzylammonium chloride)

Benzalkonium chloride (CASRN 63449-41-2) a qarternary ammonium compound used in aquaculture to disinfect equipment and holding pens.

Calcium Peroxide

Calium peroxide (CASRN 1305-79-9) is an oxidizing agent that is used to control phytoplankton, kill disease organisms and oxidize bottom soils. The main toxic concerns are acute effects from irritation at high concentrations. FDA lists calcium phosphate as an additive for some foods.

Calcium Phosphate

Calcium phosphate (CASRN 7758-87-4) is a fertilizer for phytoplankton. FDA lists calcium phosphate as an additive for some foods and for animal feed.

Calcium Sulfate (gypsum)

Calcium sulfate (CASRN 7778-18-9) is a flocculant used to cause suspended clay particles to precipitate to clear water turbidity. It is also an osmoregulator that is applied to the water to improve conditions. FDA lists calcium phosphate as an additive for some foods.

Ferric Chloride

Ferric chloride (CASRN 7705-08-0) is a flocculant used to cause suspended clay particles to precipitate to clear water turbidity. FDA lists ferric chloride as a food additive.

Methyl Mercury

Methyl mercury (CASRN 22967-92-6) is an environmental pollutant and historically was used as pesticide. Methyl mercury bioaccumulates in fish. The FDA/CFSAN Fish and Fisheries Products and Controls Guidance lists a guidance level for Methyl Mercury at 1.0 ppm for finfish. EPA has established an RfD on the basis of neurodevelopmental impairment in human epidemiological studies; the RfD includes a 10-fold uncertainty factor. EPA classifies methyl mercury as class C, possible human carcinogen.

Phosphoric Acid

Phosphoric acid (CASRN 7664-38-2) is used as a fertilizer in aquaculture. Although there is an inhalation reference concentration, EPA indicates that there is insufficient data to establish an oral RfD for phosphoric acid or to assess its carcinogenicity. FDA lists phosphoric acid as an additive for some foods and for animal feed practices.

Polychlorinated Biphenyls (PCB’s)

Manufacture of PCB’s (CASRN 1336-36-3) stopped in the U.S. in August of 1977, but residues persist and they have the ability to bioaccumulate in fish. EPA has established RfDs for individual PCBs. The FDA/CFSAN Fish and Fisheries Products and Controls Guidance lists a tolerance level for PCB’s at 2.0 ppm.

Polyvidone iodine (polyvinylpyrrolidone-iodine complex)

Polyvidone iodine (CASRN 25655-41-8) is an iodine-based disinfectant used on equipment and holding pens. It is also a widely used topical antiseptic.

Potassium nitrate/Sodium Nitrate

Potassium nitrate (CASRN 7757-79-1) and sodium nitrates (7631-99-4) are oxidizing agent used in aquaculture to control phytoplankton, kill disease organisms and oxidize bottom soils. FDA lists potassium and sodium nitrates as additives for preserving meat and poultry products.

Sodium Silicate

Sodium silicate (CASRN 1344-09-8) is used as a fertilizer for phytoplankton. It is designated by FDA as a corrosion-inhibiting compound for canned potable water. In a 2007 biopesticides registration action document EPA concluded that the "overall toxicological risk from human exposure to potassium silicate is negligible"

Trace element mixes including iron, zinc, copper, boron and molybdenum

Trace element mixes (including iron, zinc, copper, boron and molybdenum) are used as fertilizers for phytoplankton. Many of those elements are considered essential elements. EPA has established an RfD for zinc, boron and molybdenum of 0.3 mg/kg/day, 0.2 mg/kg/day and $5x10^{-3}$ mg/kg/day, respectively.

Zeolite

Zeolite (CASRN 68989-22-0) is a flocculant used to cause suspended clay particles to precipitate to clear water turbidity. The EPA does not have information on zeolite available on IRIS.

2.3 Selected Chemical Residues Detected in Siluriformes

A variety of potential chemical hazards have been detected in a limited number of catfish samples. Prevalence and concentrations of residues for some of these hazards in samples collected through 2008 are presented in Table 2. Information on additional pesticides detected by the USDA Agricultural Marketing Service's Pesticide Data Program (PDP) through 2010 has been included in the Addendum. For each analyte, the residue data for domestic and imported samples were obtained using the same analytical procedures, the same laboratories, and fish that were harvested at approximately the same time; this facilitates the comparison of residues in imported and domestic product. Combining these data in a single table is illustrative of the concentrations found, but caution should be used in drawing conclusions from this table without taking into account variations in the sample design, thus the ability to generalize the findings.

Table 2. Summary of Recent Catfish Residue Data

	% Positive	% Violative	N	Data Source	Sampling Year	LOD (ppb)	Concentration (ppb) Mean of All	Mean of Positives	Max	Regulatory Levels (ppb) U.S.	Codex
Domestic											
DDT	93%	0%	281	1	2008	1	34.4	37	651	5000	
PCB*	98%	0%	120	2	2001-2003	$1x10^{-7}$ to $1x10^{-3}$	$6.0x10^{-4}$	$6.2x10^{-4}$	$4.6x10^{-3}$	2000	
Chlorpyrifos	1%	1%	303	1	2008	1	0.0	1.8	2.6	0	
Arsenic	0%	NA	20	3	2008	200	0.0	0	0		
Cadmium	0%	NA	20	3	2008	10	0.0	0	0		
Lead	0%	NA	20	3	2008	25	0.0	0	0		300
Mercury	0%	0%	20	3	2008	100	0.0	0	0	1000	500
Malachite Green	0%	0%	16	2	2007	1	0	0	0	0	
Gentian Violet	0%	0%	2	2	2008	0.1	0	0	0	0	
Nitrofurans	ND	-	ND	-		1	ND	ND	ND	0	
Imported											
DDT	46%	0%	70	1	2008	1	3.1	6.7	53	5000	
PCB*	63%	0%	8	2	2001-2003	$1x10^{-7}$ to $1x10^{-3}$	$3.8x10^{-6}$	$6.0x10^{-6}$	$1.4x10^{-5}$	2000	
Chlorpyrifos	32%	32%	75	1	2008	1	0.9	2.9	16.4	0	
Arsenic	2%	NA	110	3	2008	200	23.6	1300	1600		
Cadmium	0%	NA	112	3	2008	10	0.0	0	0		
Lead	10%	NA	112	3	2008	25	4.1	42	77		300
Mercury	0%	0%	112	3	2008	100	0.0	0	0	1000	500
Malachite Green	9%		150	2	2007	1	1.2	12.5	122	0	
Gentian Violet	2%		53	2	2008	0.1	0.0	2.5	3	0	
Nitrofurans	ND	-	ND	-		1	ND	ND	ND	0	

*PCB data reported as toxicity equivalents; LOD varies for each congener analyzed;
Abbreviations: NA, Not Applicable; ND, No Data.
Data sources: 1)USDA-AMS 2008; 2) US FDA 2008b; and 3)USDA-FSIS, 2009.

2.4 Summary of Hazard Identification

Although not as much data are available for seafood and catfish as for other products like poultry, the studies and data reviewed in the *Prioritization of Potential Microbial Hazards* demonstrate that foodborne pathogens have been detected in seafood and, specifically, in catfish. *Listeria monocytogenes* and *Salmonella* have been detected in raw catfish samples. Listeria was detected in 5.9% to 47% of raw catfish samples in the studies. *Salmonella* was detected in either fish or specifically catfish in both research studies published in the peer review literature and in FDA's sampling program, with the percent positives in the studies ranging from 2.3% to 21%, depending on the study and the source of the catfish (domestic or imported). Given that *Salmonella* is a leading cause of foodborne illness in the United States, and the presence of *Salmonella* in catfish and fish in general, this hazard identification supports *Salmonella* as a focus of this risk assessment.

A number of chemicals that might be present on catfish are briefly reviewed in the *Identification of Potential Chemical Hazards* section. Those chemicals were identified either through testing results or by identifying chemicals that are commonly used in aquaculture. A number of the chemicals have very low toxicity and, therefore, pose little to no risk from consumption of catfish. Other chemicals, however, are associated with toxic endpoints and, if present at a high enough concentration in catfish, would have the potential to lead to health effects. Data in Table 2 indicate that some hazardous chemicals have been detected in raw catfish samples, including some at violative levels and chemicals that are not approved by the FDA for use in aquaculture. One domestic sample and 32% of imported samples had chlorpyrifos above the violative level. In addition, malachite green and gentian violet—both of which are not approved by FDA for aquaculture and for which there is evidence of mutagenicity, carcinogenicity or teratogenicity, depending on the compound—have both been detected in imported catfish samples. Arsenic and lead have also been detected in samples of imported catfish. Given the small number of test results and the low percentage of samples tested positive—and even lower number of samples above violative levels—compared with *Salmonella,* the remainder of this risk assessment focuses on estimating the potential range of risks from *Salmonella* associated with catfish consumption.

3. Model overview

Modeling annual human salmonellosis cases potentially resulting from consuming contaminated Siluriformes comprises two basic steps. First, the number of contaminated catfish (of the order Siluriformes) servings consumed each year, based on domestic production and import data, and estimates of the prevalence of *Salmonella* contamination of Siluriformes (Figure 1). Note that both inputs to this first step—the number of servings consumed and the number of fish that have *Salmonella* contamination—are estimated on the basis of very limited data. Second, the average probability of illness across contaminated Siluriformes servings is estimated by modeling contaminated servings of catfish (of the order Siluriformes) from the point of production through consumption (Figure 2). The product of these two steps estimates the annual number of human salmonellosis cases in the United States.

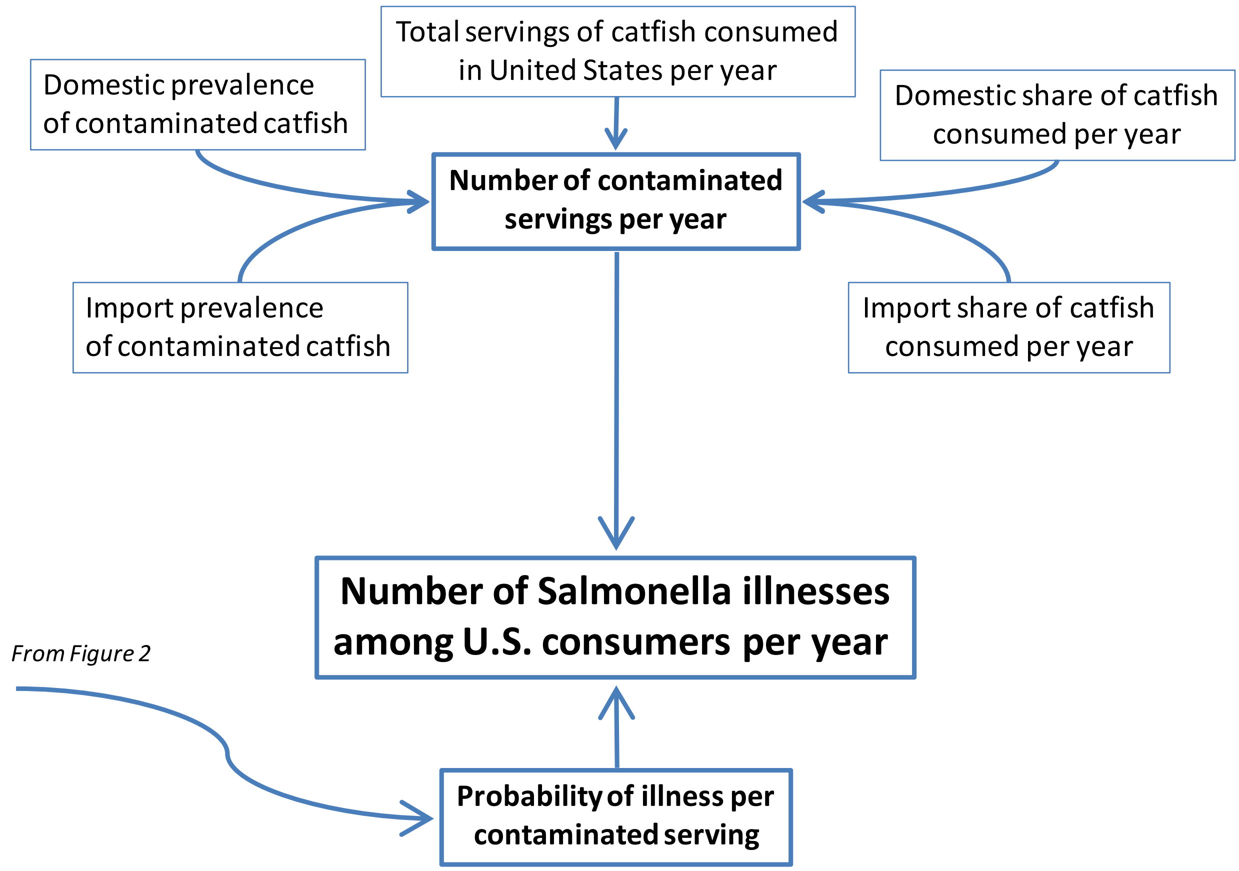

Figure 1. Inputs to number of *Salmonella* illnesses among U.S. consumers per year.

Mathematically, the first step is a simple algebraic calculation of the annual number of *Salmonella*-contaminated Siluriformes servings.

Equation 1

$$\# \text{ contaminated servings} / yr = N_{servings}\left[\left(f_{imports} \times prev_{imports}\right) + \left((1 - f_{imports}) \times prev_{domestic}\right)\right]$$

where $N_{servings}$ is the total number of servings of Siluriformes consumed in the U.S. per year, f_{import} is the fraction (share) of all servings generated by imported product, $prev_{domestic}$ and $prev_{import}$ are the proportions of domestic and imported product contaminated with some level of *Salmonella*. This modeling approach assumes that each fish carcass produces roughly the same average number of servings regardless of its contamination status. The values for these inputs are described in the Exposure Assessment section.

The model assumes each fish serving derives from a single carcass (i.e., servings are not mixtures of multiple carcasses). The model considers the average concentration of *Salmonella* (per gram of a carcass) for contaminated fish only. This concentration randomly varies among contaminated fish. It is assumed that the average concentration of *Salmonella* per gram of a contaminated fish is independent of the size of serving generated from a fish (i.e., the grams in a consumed serving does not depend on the amount of *Salmonella* per gram on the contaminated carcass). Furthermore, it is assumed that handling of the fish during retail and home storage (and cooking prior to consumption) is independent of the concentration of *Salmonella* initially on the carcass. (Because consumers will not be aware of the concentration of *Salmonella* on any particular carcass, these assumptions seem reasonable.)

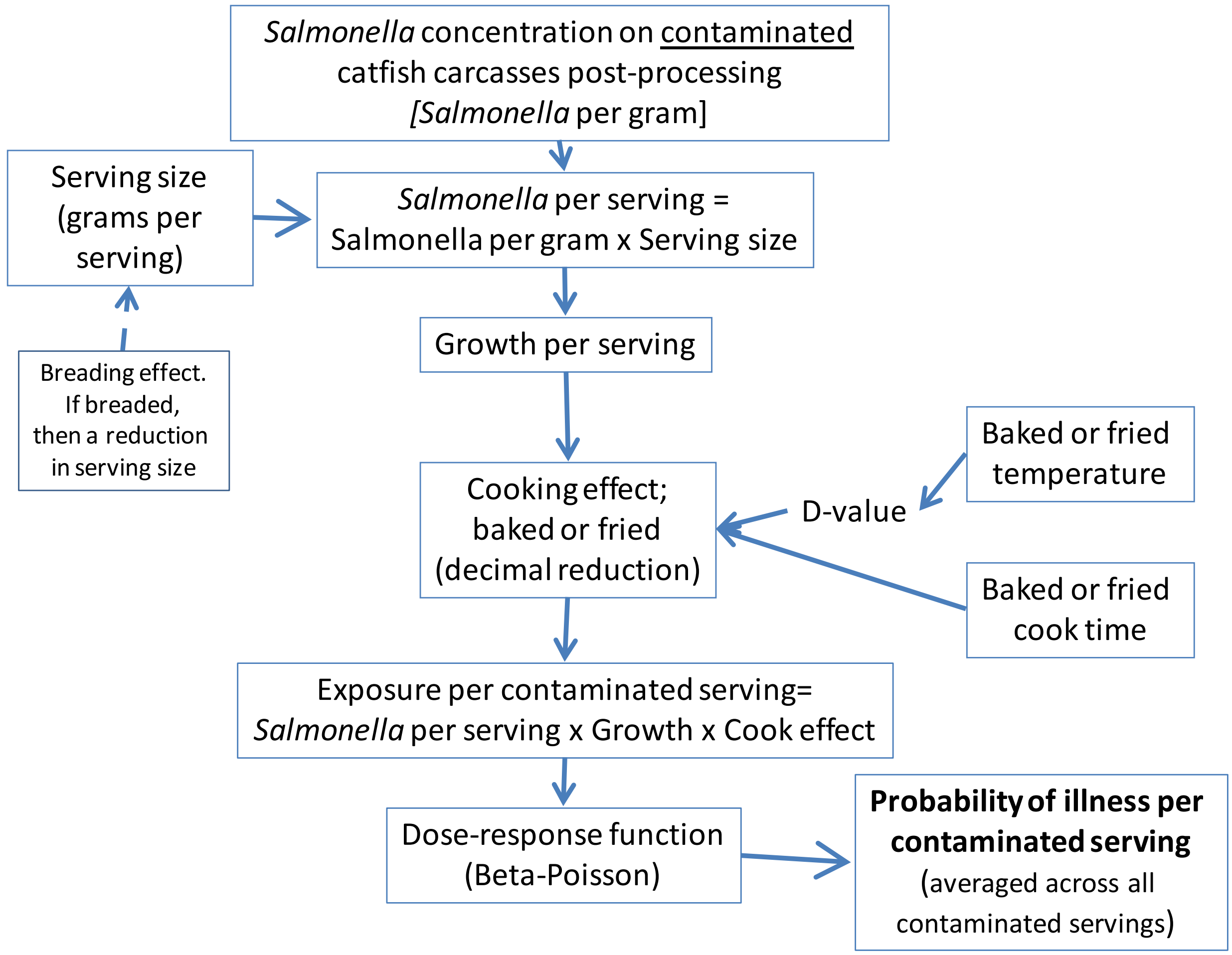

Figure 2. Inputs to probability of illness per contaminated serving.

Mathematically, the average exposure dose of *Salmonella*[31] consumed in a random contaminated 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 carcass, S is

[31] 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.

one instance of a serving size (in grams consumed), G is one instance of the growth of *Salmonella* on a 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 caused by the effects of cooking. The inputs to this calculation (X, S, G, C) are random variables. The inputs for serving size and the effect of cooking, however, are somewhat complicated.

The amount of product in a serving depends on whether the serving was breaded or not. Breaded servings contain a smaller amount of fish, on average, than non-breaded servings. Therefore, there are actually two variables for the servings – one for breaded servings (S_{Bread}) and one for non-breaded servings ($S_{Nonbread}$).

The effect of cooking depends on the method used. Baking tends to involve longer cook times than frying. Therefore, there are two variables to differentiate the type of cooking used – one for baked servings (C_{Baked}) and one for fried servings (C_{Fried}).

A dose-response relationship is used to predict the probability of salmonellosis for each serving contaminated with *Salmonella*. There are four categories of product exposures assessed:

1. Breaded and baked ($D_{Bread,Baked}$);
2. Breaded and fried ($D_{Bread,Fried}$);
3. Non-breaded and baked($D_{Nonbread,Baked}$); and
4. Non-breaded and fried ($D_{Nonbread,Fried}$).

For each category of product consumed, the average probability of salmonellosis across all contaminated servings within the class is determined as:

Equation 3 $$P_{b,c}(ill) = \frac{1}{n}\sum_{i=1}^{n}\left[1-\left(1-\frac{D_{b,c_i}}{\beta}\right)^{-\alpha}\right]$$

where n is the number of iterations of the Monte Carlo model, and b and c symbolize the breading and cooking indexes, respectively. This calculation is a numeric integration assuming a beta-Poisson dose-response function with parameters α and β .

Given the preceding discussion, the annual number of human salmonellosis cases from catfish (of the order Siluriformes) exposure is estimated as:

Equation 4

$$Number\_ill/yr = \#contaminated\ servings/yr \times \begin{bmatrix} f_{Bread} \times f_{Baked} \times P_{Bread,Baked}(ill) + \\ f_{Bread} \times (1 - f_{Baked}) \times P_{Bread,Fried}(ill) + \\ (1 - f_{Bread}) \times f_{Baked} \times P_{NonBread,Baked}(ill) + \\ (1 - f_{Bread}) \times (1 - f_{Baked}) \times P_{NonBread,Fired}(ill) \end{bmatrix}$$

where f_{Bread} is the fraction of servings that are breaded and f_{Baked} is the fraction of servings that are baked.

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 across all four exposure pathways.

4. Exposure Assessment

The exposure assessment estimates the annual exposures to *Salmonella* from catfish (of the order Siluriformes) consumed in the U.S. Model inputs for the exposure assessment are explained in the following sections. The Siluriformes-associated hazard concentration section describes the development of the inputs X, $prev_{domestic}$, and $prev_{imports}$. The storage and cooking effect section considers the effects of G, C_{Baked}, and C_{Fried}. The section on product consumption describes the development of the inputs S_{Bread}, $S_{Nonbread}$, $f_{Breaded}$, f_{Baked}, $f_{imports}$, and $N_{servings}$.

4.1 Siluriformes-associated Hazard Concentration (X, $prev_{domestic}$, and $prev_{imports}$)

No empiric evidence regarding concentrations of *Salmonella* on processed Siluriformes carcasses was available and limited evidence was available regarding the prevalence of *Salmonella* contaminated catfish of the order Siluriformes. One U.S. study collected 220 catfish fillets from August 1994 through May 1995 (McCaskey et al., 1998). That study found 5 (2.3%) positive samples. This evidence was used to represent the default prevalence of *Salmonella* contamination of catfish ($prev_{domestic}$) in the model.

Although the FDA's Office of Regulatory Affairs/Office of Regulatory Science (formerly the Office of Regulatory Affairs/Division of Field Science) collects some samples of imported catfish, those samples are pooled samples of multiple catfish homogenized for regulatory testing. Furthermore, the samples are intentionally targeted towards imported shipments thought to have a higher probability of testing positive. The pooled and biased nature of these data would likely over-estimate the prevalence of *Salmonella* contamination of catfish (of the order Siluriformes) consumed in the U.S. Furthermore, these inherent sampling and *Salmonella* testing biases make reasonable inferences about *Salmonella* prevalence among imported product from FDA data nearly impossible. Lacking any other evidence regarding *Salmonella* prevalence on imported product, this risk assessment assumed that the prevalence of *Salmonella* on imported product is the same as the prevalence of *Salmonella* found on domestic product (i.e., a default assumption that $prev_{imports} = prev_{domestic}$).

While there is limited data on the prevalence of *Salmonella*-contaminated catfish of the order Siluriformes, there is no data on the amount (concentration) of *Salmonella* per gram of these fish. Therefore, the concentration of *Salmonella* on contaminated product model input X , is assumed to be reflected by available *Salmonella* enumeration results from FSIS poultry (i.e. broiler) testing programs. There are limitations with the use of poultry *Salmonella* testing data as a surrogate that impact what we might see after implementing an inspection program for Siluriformes. However, such data are the best option available for such an analysis because:

1. Of the species FSIS currently regulates, poultry represent a surface area to mass ratio that most closely approximates this ratio for Siluriformes.
2. *Salmonella* testing methods for poultry would more nearly approximate those used for Siluriformes (i.e., both methods use whole carcass rinsing) than testing results for other species that FSIS regulates. Also, the enumeration of *Salmonella* concentrations on poultry using these methods makes extrapolation to *Salmonella* per carcass more intuitive compared to cattle or hog carcass sampling techniques that do not involve rinse sampling of the entire carcass surface area.
3. Poultry processing typically involves a carcass chilling step that requires submersion of carcasses in water that might reflect the potential cross-contamination that can occur in the aquatic environment of these fish.

Although use of poultry concentration data as a surrogate for Siluriformes concentration data is arguable, the concept that *Salmonella* contamination levels on Siluriformes are variable is crucial to assessing risk. Ignoring this variability in the risk assessment would potentially undervalue the risk posed to consumers because catfish (of the order Siluriformes) servings with larger concentrations of *Salmonella* might not be considered.

The FSIS nationwide broiler chicken microbiological baseline data from 1994-1995 were used to estimate *Salmonella* concentrations on catfish (of the order Siluriformes)

(USDA-FSIS, 1996). This survey was chosen because it represented a snapshot of the poultry industry prior to the formal implementation of a new FSIS inspection program (HACCP). The current regulatory decision for the Siluriformes industry is similar to the decision made in the mid-1990s for broiler poultry and other FSIS-regulated species in that a new FSIS program will be implemented. The existing regulatory program under FDA serves as the baseline protection of food safety, upon which the new FSIS inspection program will be built. Because this risk assessment is designed to predict human illnesses avoided following implementation of a new FSIS-style regulatory system within the Siluriformes industry, it seems appropriate to consider the status of the broiler poultry industry prior to the implementation of HACCP by FSIS.

The broiler poultry data imply that most contaminated carcasses have low *Salmonella* concentrations (Table 3). For this analysis, positive broiler poultry samples with a Most Probable Number per milliliter (MPN/ml) values <0.03 (i.e., below the limit of enumeration) were assumed to be uniformly distributed between 0.0025 MPN/ml (i.e., the assumed absolute lower limit of qualitative detection in a 400 ml chicken rinse sample) and 0.03 MPN/ml. For *Salmonella* concentrations greater than 0.03 MPN/ml, values are randomly distributed according to the data summarized in Table 3[32]. To adjust these data to units of *Salmonella* per gram of Siluriformes, the following calculation was completed:

Equation 5
$$Salmonella \big/ gram = \frac{MPN}{ml} \times 400ml \times \frac{1}{1500g}$$

This calculation indicates that the *Salmonella* concentration per ml of rinse is expanded by the 400 ml rinse volume to estimate total MPN per carcass; this total is then divided by 1,500 grams to account for the average weight of a broiler poultry carcass.

Broiler poultry rinse samples typically come from skin-on carcasses. Evidence suggests that pathogen concentrations are 0.4 to 0.9 logs less for skinless poultry carcasses (Davis and Conner, 2007; Berrang et al., 2002). Because these fish are

[32] Initial attempts to fit these data to parametric distributions suggested a poor fit. Therefore, this risk assessment uses an empirical cumulative distribution based on the data in Table 3 to model variability in *Salmonella* concentration.

generally sold skinless, broiler poultry concentrations are translated to fish concentrations by adjusting for the skinless carcass. As a default, it is assumed that Siluriformes *Salmonella* concentrations are 0.65 logs (midway between 0.4 and 0.9) less than poultry concentrations. This step is modeled by multiplying the value obtained in Equation 5 by 0.22 ($10^{-0.65} = 0.22$).

Equation 6 $$Salmonella/gram_{NoSkin} = \frac{MPN}{ml} \times 400ml \times \frac{1}{1500g} \times 0.22$$

One last adjustment truncates the distribution of *Salmonella* concentration on Siluriformes at a minimum of 1 colony forming unit (CFU) per 330 gram to represent the average weight of a carcass (Morris, 1993)[33]. For a default assumption, any concentration resulting from the adjusted broiler poultry data that is less than 0.003 CFU/g is assumed to equal 0.003 CFU/g. Nevertheless, in scenarios exploring uncertainty, the risk assessment model randomly redistributes concentrations less than 0.003 CFU/g to values above that threshold.

Table 3. Summary of *Salmonella* concentrations in enumerated positive broiler carcass rinse samples (USDA-FSIS Nationwide Broiler Chicken Microbiological Baseline Data Collection Program, 1994-1995)

Range (MPN/ml)	Number of Samples	Cumulative Percent
<0.03	109	41.9
0.03 – 0.30	118	87.3
0.301 - 3.0	24	96.5
3.01 - 30.0	6	98.8
>30.0	3	100.0
Total	260	

[33]It is assumed that the average catfish marketed in the U.S. is 1.44 pounds (http://usda.mannlib.cornell.edu/usda/nass/CatfProd//2000s/2009/CatfProd-01-30-2009_revision.pdf) and an average dressing percentage of 50% (Morris, 1993).

The resulting random variable X (average *Salmonella* per gram of contaminated carcass) estimates that 64% of contaminated carcasses have *Salmonella* concentrations of 0.003 per gram (the theoretic minimum level) (Table 4). Because a serving generally represents something less than the entire carcass weight, the amount of *Salmonella* actually in a serving could be less than one *Salmonella* bacterium. The maximum concentration of *Salmonella* on a carcass is estimated to be 16.7 bacteria per gram. For comparison, the maximum concentration for broiler poultry was ~75 *Salmonella* per gram[34].

Table 4. The estimated distribution of *Salmonella* per gram of contaminated fish carcass.

Cumulative frequency	*Salmonella* per gram of fish carcass	Average *Salmonella* per carcass*
0%	0.003	1
64%	0.003	1
68%	0.005	2
75%	0.006	2
76%	0.007	2
80%	0.010	3
81%	0.013	4
82%	0.014	5
87%	0.016	5
90%	0.029	10
91%	0.030	10
92%	0.039	13
95%	0.064	21
96%	0.157	52
97%	0.417	139
98%	1.006	335
99%	2.106	701
100%	16.715	5,566

* Average *Salmonella* per carcass is estimated by assuming each carcass weighs 333 grams

[34] The maximum *Salmonella* MPN/ml from the USDA-FSIS 1994-1995 baseline study was 280. The maximum implied a *Salmonella* concentration per gram of chicken of: $\frac{280 MPN}{ml} \times \frac{400 ml}{1500 g} = 74.7 MPN / g$.

4.2 Storage and Cooking Effect (G, C_{Baked}, and C_{Fried})

Salmonella concentrations on raw processed Siluriformes at the point of consumption are adjusted to account for concentration changes associated with both potential storage and potential cooking scenarios. Microbial hazard concentrations may increase during storage and preparation and typically decrease during cooking. Specific modifying factors for *Salmonella* were calculated based on cooking style (e.g. baked versus fried). Because specific evidence regarding *Salmonella* growth and cooking effects is not available for these products, modeling techniques from a published risk assessment regarding *Salmonella* in chicken were used for these factors (Oscar, 2004).

Variability of growth multiplication and cooking decimal reductions was based on *Pert* (min, most likely, max) distributions for log growth, cooking time, and cooking temperature (Table 5). The *Salmonella* growth model and parameters were adopted directly from predictive microbial models for chicken developed by Oscar (2004); that model includes the assumption that growth could only occur among 0.02% of servings. The cooking model was also based on Oscar (2004), but time and temperature parameters for baking or frying were based on expert opinion and review of several on-line cooking recommendations.

Table 5. Parameters for cooking and growth inputs

Factor	Equation	Cooking Type	Parameters		
			Min	Most likely	Max
Cooking	$C = \dfrac{1}{10^{\left(\frac{Pert\left(\frac{min}{time}, \frac{most\ likely}{time}, \frac{max}{time}\right)}{10^{\left(8.7344 - \left(0.1316 * Pert\left(\frac{min}{temp}, \frac{most\ likely}{temp}, \frac{max}{temp}\right)\right)\right)}}\right)}}$	Baked (minutes)	12.00	13.50	15.00
		Baked (°C)	58.75	64.20	69.70
		Fried (minutes)	6.00	9.00	12.00
		Fried (°C)	58.75	64.17	69.70
Growth	$G = 10^{Triangle(min,\ most\ likely, max)}$	All methods	0	0.04	0.15

The random variable for growth effect (G) estimates 99.98% of servings are unchanged between processing and consumption (Table 6). The remaining small fraction of contaminated servings in which growth occurs experience a 10% to 40% increase in the number of *Salmonella* within the serving.

Table 6. The distribution of growth effect multiplier per serving (G) estimated by the model is shown.

Cumulative Frequency	Growth Effect Multiplier
0.000%	1
99.970%	1
99.980%	1.1
99.992%	1.2
99.999%	1.3
100.000%	1.4

The reduction in *Salmonella* per serving caused by baking (C_{Baked}) extends from nearly 1.2 logs to nearly 40 logs (Figure 3). The logs of the median and mean reductions are about 7 and 3, respectively.

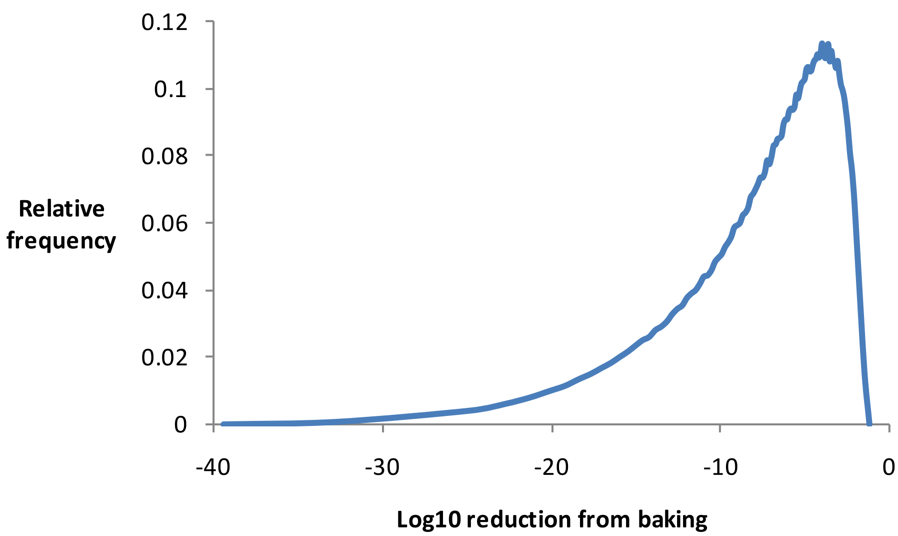

Figure 3. Log reductions of *Salmonella* due to baking.

The reduction in *Salmonella* per serving caused by frying (C_{Fried}) extends from less than 1 log to nearly 30 log (Figure 4). The log of the median and mean reductions are about 4.5 and 2, respectively.

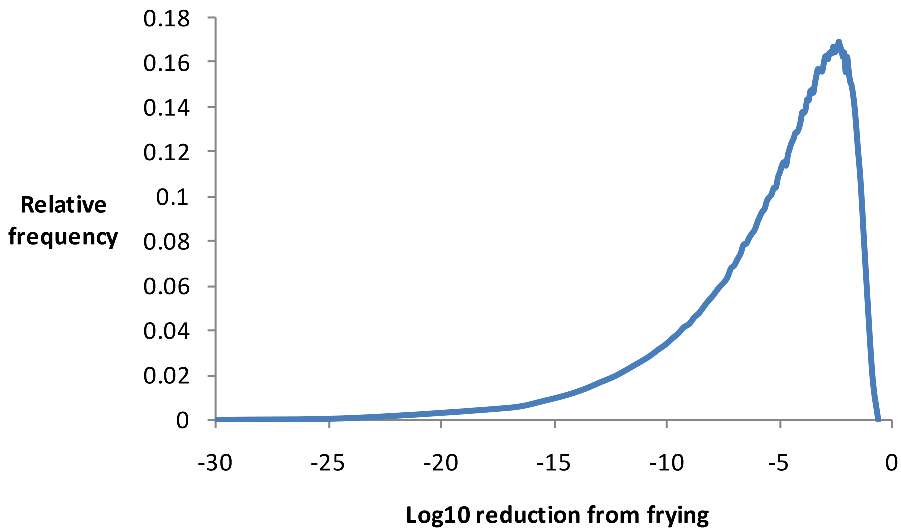

Figure 4. Log reductions of *Salmonella* due to frying.

4.3 Product Consumption (S_{Bread}, $S_{Nonbread}$, f_{Bread}, f_{Baked}, $f_{imports}$ and $N_{servings}$)

Data on the consumption of catfish[35] in the U.S. were obtained from the National Health and Nutrition Examination Survey (NHANES). Four 2-year consumption survey data sets (1999-2006) of total size 41,474 were combined to create an 8-year data file of single 24-hour consumption recall estimates and a combined 4-year file of two 2-year datasets (2003-2006) of total size 20,471, with first and second day 24-hour recall estimates. The 8-year file of consumption data was taken from the 1-day mobile examination center (MEC) face-to-face interviews and used 8-year MEC weights permitting standardization of the sample results to the 2000 U.S. census. Estimates were made for the U.S. population at the midpoint of the 8-year survey period using SAS-Callable SUDAAN

[35] National Health and Nutrition Examination Survey (NHANES).did not specify the fish beyond *catfish* so this term is used in this section to be consistent with the original reference.

software (version 10, Research Triangle Institute International, Research Triangle Park, NC). Similarly, the 4-year dataset used the MEC examination and interview results for the first 24-hour recall and a second telephone interview 24-hour recall within 3 to 10 days of the first interview. The 2-day NHANES weights, corrected for post stratification and non-response, were used in the 4-year dataset analysis. Each dataset was validated for completeness and 2122 subjects were eliminated from the calculations leaving 39,352 validated subjects in the 8-year dataset, 18,382 validated subjects in the first day of the 4-year dataset, and 16,781 validated subjects in the second day of the 4-year dataset.

The 8-year dataset provided 249 consumers of catfish, while the 4-year one and two day combined datasets provided 125 and 110 consumers respectively. In the latter study, only 8 subjects were validated for both first and second day interviews. The 8-year dataset provided the estimate for grams of catfish consumed per day, which did not differ significantly from the combined 4-year dataset estimate. The estimates for the fractions of baked and breaded catfish consumed and annual percent catfish consumers were made from the combined averaged data over all survey years and interview days.

Two datasets were evaluated because of the low frequency of catfish consumers in the survey population and the motivation to find the best dataset. The NHANES priority was to over-sample women, children, and minorities requiring a multi-stage sampling design for estimation of U.S. population mean and standard error of the total daily grams of catfish consumption and the fractions of baked and breaded catfish consumed. Because the second day data did not sufficiently provide within subject variability estimates due to only eight persons actually validated for both first and second day interviews, a correction for the averaged first and second day responses was assessed by simulation using the SUDAAN “HOTDECK” procedure to produce estimates of between and within subject error providing the necessary factors for reducing increased variance bias using the National Research Council (1986) recommendation for bias correction. Additionally, the recommended procedure for estimating nutrient intake from complex survey data was employed (Nusser et al., 1996).

Due to the smaller sample size, the mean, variance, and percentile estimates for daily grams catfish consumed for the combined 4-year dataset were not significantly different from the 8-year dataset using standard T-tests for the mean, F-tests for variance, and the Kolmogorov-Smirnov two-sample test for distribution shape at 95% confidence. The standard Taylor series linearized estimates from the SUDAAN DESCRIPT procedure provided the smallest error estimates compared with the internal validation methods employed. The validation methods were Jackknife (N-1) (SUDAAN proc DESCRIPT), balanced repeated replication (Fay's modified BRR in WesVar, Westat, Inc. Rockville, MD 2008), and the Rao-Wu-Yue bootstrap (Rao et al., 1992). Each of the validation methods provided mean and percentile estimates that were within the 95% confidence intervals of the Taylor series estimates. However, the variance estimates showed significantly more variability and were each contained only within the 99% confidence interval. This type of variability was expected and did not affect the risk model since the mean estimate for grams catfish consumed per day was used which was shown to be stable.

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 (1^{st} and 99^{th} 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.

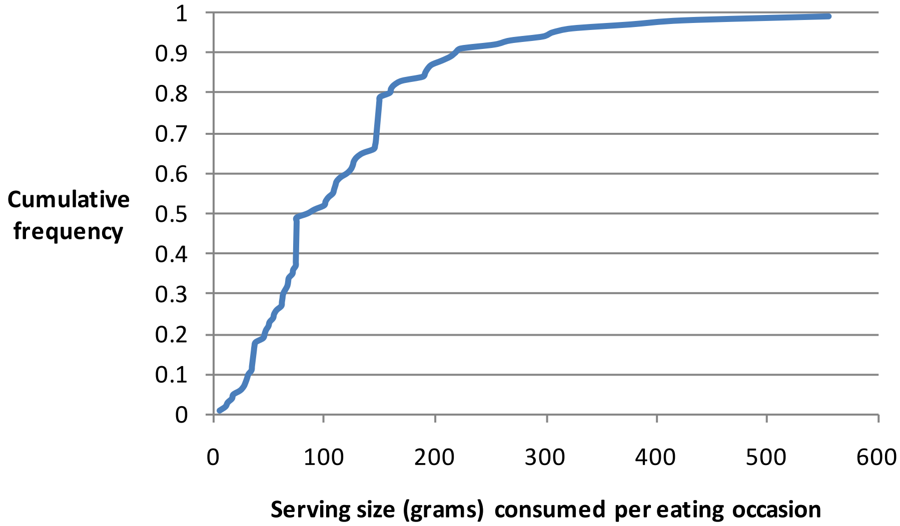

Figure 5. The cumulative empirical distribution for serving size.

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 U.S. 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 (TAES, 1989). 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.

Data from 2008 regarding total sales of catfish products were summarized (USDA-NASS, 2009). These data were adjusted slightly to estimate the proportion of amount sold that was catfish meat. For example, whole dressed and steak cuts were assumed to be 67.5% and 80% edible meat, respectively. In contrast, fillets and nuggets were assumed to represent 100% edible meat.

The combination of total domestic sales and total imported catfish in 2008 was assumed to represent the total quantity of catfish consumed annually (Table 7). Imported catfish were reported by type; *Ictalurus*, *Pangasius* and other Siluriformes. Imports constitute a smaller fraction of total *Ictalurus* $\left(f_{imports} = \frac{10,470,953}{116,150,192} \approx 9\% \right)$ than total Siluriformes $\left(f_{imports} = \frac{46,276,651}{151,955,889} \approx 30\% \right)$. Also, total Ictaluridae catfish available for consumption represent about 76% $\left(\frac{116,150,192}{151,955,889} \right)$ of all fish in the order Siluriformes.

Table 7. Kilograms of varieties of catfish available for consumption in the United States, 2008.

Origin	*Ictalurus*	*Pangasius*	Other Siluriformes	Total
Imported	10,470,953	35,748,529	57,169	46,276,651
Domestic	105,679,239	0	0	105,679,239
Total	116,150,192	35,748,529	57,169	151,955,889

Given the estimates for average serving size and total catfish consumed, the total number of catfish servings $\left(N_{servings} \right)$ is estimated (Table 8). Nevertheless, average serving size is adjusted to account for the fraction of servings that are breaded (i.e., serving size reported by consumers includes the breading material, while catfish sales does not include breading). The average serving size of catfish (adjusted for breading material) is calculated as follows:

$$Avg.\,serving\ size = Serving\_size_{NHANES} \left[\left(1 - f_{Bread} \right) + f_{Bread} \times Bread\_effect \right] = 98.13 grams$$

Table 8. Mean Estimates of Catfish Servings

Catfish definitions	Mean Serving Size (g)[1]	Annual U.S. Catfish Consumption (kg)[2]	Annual U.S. Catfish Servings[3]
Siluriformes	98.13	151,955,889	1,548,519,606
Ictaluridae	98.13	116,150,192	1,183,638,553

[1] Calculated from NHANES data
[2] Domestic and import catfish production data
[3] Annual U.S. Catfish Consumption divided by Mean Serving Size

5. Hazard Characterization (Dose-Response)

The dose-response equation described by the World Health Organization and Food and Agriculture Organization (WHO/FAO, 2002) was used to estimate the probability of illness resulting from exposure to *Salmonella* in a single serving of Siluriformes. The dose-response function is:

Equation 7 $$P(ill\,|\,exp) = 1 - \left(1 + \frac{D}{\beta}\right)^{-\alpha}$$

with parameters ($\alpha = 0.1324$, $\beta = 51.45$).

This dose-response relationship is assumed to be the same for all humans exposed (i.e., regardless of age, sex or susceptibility) and all *Salmonella* strains. Although such assumptions are arguable, this relationship represents an international guideline that is assumed adequate for estimating effects across whole populations of consumers. Nevertheless, assessing the risk for specific consumers or classes of consumers might benefit from adjustments to this dose-response relationship.

6. Risk characterization

The model that is used to estimate the risk of *Salmonella* illness potentially associated with the estimated catfish (of the order Siluriformes) consumption distribution combines the exposure assessment with the hazard characterization. Equations 1 – 4 outline the mathematics of this process.

This section will present the default model (baseline) estimation for the annual number of human cases of salmonellosis potentially associated with catfish (of the order Siluriformes) consumption. This estimation, which is characterized by a substaintial amount of uncertainty, stems from the number of exposures generated from estimates of contaminated product and the average probability of illness among those exposures.

The analysis also compared the modelled estimation of annual *Salmonella* illnesses associated with these fish with estimates based on the available public health surveillance (i.e., epidemiological) information. Estimates of total annual cases of human salmonellosis from all sources are adjusted by the fraction of cases attributable to Siluriformes.

Because the ultimate purpose of this risk assessment is to inform regulatory decision-making, this report focuses on the approach taken to model the effectiveness of an FSIS inspection program in reducing the annual burden of human illness. This section of risk characterization provides a description to illustrate how FSIS seeks to improve food safety for Siluriformes, as well as describing the mathematics, input data and uncertainty associated with modeling the effectiveness of an FSIS Siluriformes inspection program.

Estimates of the potential effectiveness of an FSIS Siluriformes inspection program are presented relative to the default annual number of *Salmonella* illnesses estimated to be currently associated with these fish. Even allowing for significant uncertainty about the baseline number of annual illnesses, substantial uncertainty remains about the level of effectiveness that can be achieved by FSIS inspection and the rate at which the effectiveness can be achieved.

The final sections of risk characterization examine the sensitivity of the estimated number of *Salmonella* illnesses associated with these fish to some changes in the risk assessment model inputs and the effects of this uncertainty about inputs on model estimates. Several scenarios are examined to explore the potential error in predictions caused by influential and highly uncertain risk assessment model inputs.

6.1 Default estimation of numbers of *Salmonella* illnesses per year using the process model

The computer model comprises 3 million iterations. By running the model multiple times, it was determined that the estimated number of illnesses per year stabilized such that there was a 95% confidence that any simulation using the chosen input parameters was within ~2.5% of the average estimate calculated across the multiple simulations of 3 million iterations each.

A seed value was used for sensitivity and scenario analyses that generated an annual number of illnesses equivalent to the mean across multiple simulations. This approach allowed a direct comparison between the estimated numbers of illnesses using the model's default settings and alternative settings.

For the default model settings, the number of contaminated servings per year was 30,970,392 using the Siluriformes definition of catfish. This number determines the servings generated from *Salmonella*-contaminated product; it represents the annual potential exposures to *Salmonella*. If catfish are defined as Ictaluridae, then 23,673,768 contaminated servings per year are estimated. The difference in contaminated servings is determined solely by the share of Ictaluridae among Siluriformes.

Exposures from contaminated servings are determined using the average *Salmonella* dose per exposure. A dose-response function determines the probability of illness for each exposure dose. The probability of illness per contaminated serving for each combination of cooking and breading is generally very small (Table 9) with, for example, the 75th percentiles suggesting the probability of illness is less than 1.6 in one million for contaminated servings. The maximum probability of illness across all exposures is 0.35; for the default beta-Poisson dose-response function, this probability of illness corresponds to a maximum dose of 1,280 *Salmonella* in a serving. The mean probability of illness is slightly larger for non-breaded servings than breaded servings because serving size is larger for non-breaded servings. The mean probability of illness is somewhat larger for fried than baked servings because cooking time for frying is generally less than baking; therefore, baked servings usually involve more reduction of *Salmonella* prior to consumption than fried servings.

The modeled estimates of *Salmonella* illnesses per year using the Siluriformes and Ictaluridae definitions are 2,308 and 1,764, respectively. Because *Salmonella* prevalence among domestic and imported product is assumed to be equal in the default model settings, the number of Ictaluridae-associated annual illnesses is simply 76% of the number of Siluriformes-associated illnesses. Therefore, there is no significant difference between Siluriformes and Ictaluridae in the risk of salmonellosis *per serving*; rather the amount of total illnesses depends on the total volume of these fish consumed in the U.S. (Table 10).

Table 9. Model outputs for the estimated probability of illness per contaminated serving for the combinations of cooking and breading effects.

Probability of *Salmonella* illness per Contaminated Serving	**Minimum**	**25th percentile**	**Median**	**Mean**	**75th percentile**	**Maximum**	**Standard Deviation**
Baked and non-Breaded	0.0^{0}	$8.2\text{x}10^{-15}$	$1.2\text{x}10^{-10}$	$2.1\text{x}10^{-5}$	$5.3\text{x}10^{-8}$	$2.2\text{x}10^{-1}$	$7.9\text{x}10^{-4}$
Fried and non-Breaded	0.0	$4.3\text{x}10^{-11}$	$2.8\text{x}10^{-8}$	$1.1\text{x}10^{-4}$	$1.6\text{x}10^{-6}$	$3.5\text{x}10^{-1}$	$2.5\text{x}10^{-3}$
Baked and Breaded	0.0	$6.2\text{x}10^{-15}$	$9.3\text{x}10^{-11}$	$1.6\text{x}10^{-5}$	$4.0\text{x}10^{-8}$	$2.0\text{x}10^{-1}$	$6.4\text{x}10^{-4}$
Fried and Breaded	0.0	$3.2\text{x}10^{-11}$	$2.1\text{x}10^{-8}$	$8.8\text{x}10^{-5}$	$1.2\text{x}10^{-6}$	$3.2\text{x}10^{-1}$	$2.1\text{x}10^{-3}$

Table 10. Estimates for annual *Salmonella* illnesses for each definition of catfish.[a]

Definition of Catfish	Number of Contaminated Servings (Exposures)	Estimated Average Probability of Illness per Contaminated Serving	Estimate of *Salmonella* Illnesses per Year
Siluriformes	30,970,392	$7.452\text{x}10^{-5}$	2,308
Ictaluridae	23,673,768	$7.452\text{x}10^{-5}$	1,764

[a]Estimates derived using the process model.

On the basis of total servings consumed, the average probability of illness per serving is $\frac{2,308 \text{ illnesses/yr}}{1,548,519,606 \text{ servings/yr}} = 1.5\times10^{-6}$. This probability incorporates the prevalence of estimated contaminated servings and suggests that *Salmonella* illness resulting from consuming a serving of such fish is an uncommon event.

6.2 Illnesses per year: Application of an Attribution-Based Modelling Approach

Salmonella illnesses attributable to Siluriformes are rare. In the past 20 years there has been only one suspected outbreak reported (10 illnesses in May 1991 associated with a restaurant in New Jersey). Furthermore, Siluriformes consumption has not been identified as a factor in epidemiological (specifically, case–control) studies of salmonellosis. Nevertheless, it is possible that there is a low level of sporadic cases of salmonellosis associated with catfish (of the order Siluriformes) occurring in the U.S. which are not detected with current levels of surveillance.

The Centers for Disease Control and Prevention (CDC) lists annual reports of foodborne outbreaks from 1990 through 2007 (U.S. CDC, 2009). These reports show there are a little more than 100 outbreaks of salmonellosis in the U.S. each year. Approximately 60% of these outbreaks have a vehicle identified (Table 11). These data are used to determine an alternative estimate for the number of Siluriformes-related *Salmonella* illnesses each year. This estimation multiplies the fraction of foodborne outbreaks with identified vehicles that were attributed to Siluriformes by the estimated total *Salmonella* illnesses per year.

Table 11. ***Salmonella*** **Foodborne Outbreaks from 1990 through 2007**

Year	***Salmonella*** **Outbreaks**	**Vehicles Identified**	**%**
1990	138	82	59.4%
1991	123	64	52.0%
1992	80	48	60.0%
1993	95	62	65.3%
1994	88	52	59.1%
1995	94	51	54.3%
1996	80	47	58.8%
1997	80	54	67.5%
1998	124	62	50.0%
1999	113	77	68.1%
2000	112	76	67.9%
2001	112	78	69.6%
2002	109	74	67.9%
2003	108	70	64.8%
2004	123	64	52.0%
2005	94	67	71.3%
2006	116	62	53.4%
2007	135	69	51.1%
Total	**1,924**	**1,159**	**60.2%**

If it is assumed that the proportion of all *Salmonella* illnesses caused by a vehicle is equivalent to the proportion of outbreaks caused by that vehicle, then the expected proportion for any given year (p_t) using the evidence from the previous year would be

Equation 8 $$p_t = \frac{s_{t-1}+1}{n_{t-1}-s_{t-1}+2}.$$

where p_t is the mean of a beta distribution (Vose, 2000), s_{t-1} is the number of outbreaks caused by a particular vehicle in the previous year and n_{t-1} is the number outbreaks in the previous year.

For 2007, given 69 outbreaks in which the vehicle was identified to <u>not</u> be Siluriformes, the value of p_t would be 0.014. It would be reasonable, however, to include evidence from earlier years. The expected proportion for any given year using the evidence from *m* previous years would be

Equation 9 $p_t = \dfrac{\left(\sum_{i=1}^{m} s_{t-i}\right)+1}{\left(\sum_{i=1}^{m} n_{t-i} - s_{t-i}\right)+2}$.

If the entire set of reports from CDC is used, then there is one outbreak in which catfish is identified as vehicle and 1158 outbreaks in which other vehicles were identified. The expected value for p_t is 2/1160 = 0.0017. The 95% confidence limits associated with this proportion are from 0.0002 to 0.0048.

Mead et al. (1999) estimates there are about 1.4 million illnesses due to *Salmonella* annually. If the proportions calculated above are multiplied by 1.4 million, the estimated number of annual human illnesses is 2,400, with a lower limit of 280 and an upper limit of 6,700.

6.3 Modeling program effectiveness

Traditionally, FSIS has monitored the food safety performance of an industry based on a reduction in the prevalence of a pathogen on specific food products. Although monitoring the number (concentration) of pathogens on carcasses is an alternative and advantageous approach, laboratory enumeration of pathogen levels on carcasses is cumbersome and generally non-routine.

In the risk assessment model, it is assumed that the effect of FSIS inspection will be some reduction in the estimated prevalence of *Salmonella*-contaminated carcasses. Although FSIS inspection may also influence the number (concentration) of *Salmonella* on any contaminated carcasses, that effect is not modeled.

For the purposes of this model, it is assumed that the effect of FSIS inspection will be equivalent for domestic and imported product, consistent with import regulations that establish equivalency in food safety risk between imports and products of domestic origin.

Given these assumptions, the number of human salmonellosis illnesses associated with Siluriformes avoided each year is predicted with Equation 1 and Equation 4. The effectiveness of FSIS inspection may be some fraction, g_{FSIS}, of the default estimated prevalence of contaminated carcasses. For example, if $g_{FSIS} = 0.1$, then a 10% reduction in prevalence of contaminated carcasses following implementation of FSIS inspection is expected. Similarly, the new *Salmonella* prevalence of contaminated carcasses can be modeled by multiplying the default prevalence (i.e., 2%) by $\left(1 - g_{FSIS}\right) = 0.9$. Because the estimated number of contaminated servings per year is linear with respect to g_{FSIS}, predicting the annual illnesses avoided is a simple calculation;

$$Number\_ill\ \textbf{avoided}\ /\ yr =$$

$$\#contaminated\ servings\ \textbf{avoided}\ /\ yr \times \begin{bmatrix} f_{Bread} \times f_{Baked} \times P_{Bread,Bakedd}(ill) + \\ f_{Bread} \times \left(1 - f_{Baked}\right) \times P_{Bread,Fried}(ill) + \\ \left(1 - f_{Bread}\right) \times f_{Baked} \times P_{Nonbread,Baked}(ill) + \\ \left(1 - f_{Bread}\right) \times \left(1 - f_{Baked}\right) \times P_{Nonbread,Fried}(ill) \end{bmatrix}$$

with

$$\#\ contaminated\ servings\ \textbf{avoided}\ /\ yr =$$
$$N_{servings}\left[\left(f_{imports} \times \left[g_{FSIS} \times prev_{imports}\right]\right) + \left((1 - f_{imports}) \times \left[g_{FSIS} \times prev_{domestic}\right]\right)\right]$$

Or, given a default number of human salmonellosis cases associated with Siluriformes estimated to occur prior to an FSIS inspection program ($Number\_ill\ /\ yr$), the illnesses avoided by an FSIS cafish inspection is simply;

Equation 10 $Number\_ill\ \textbf{avoided}\ /\ yr = g_{FSIS} \times Number\_ill\ /\ yr$

Given the nature of Equation 10, it is reasonable to imagine the annual number of human salmonellosis cases from Siluriformes as a binomial process. In other words, there are a number of *Salmonella*-contaminated servings (i.e., number of trials, *n*) and each serving has an independent probability of resulting in human illness (i.e., a probability of "success", *p*). Furthermore, given a large number of servings run through the model (trials) and a small probability of human illness (defined as a "success" in terms of mathematical probabilities), this binomial process can be approximated as a Poisson process with rate parameter $\lambda = n \times p$ (Vose, 2000). This development allows an appreciation of the nature of the model's estimated annual cases. These estimated cases can be assumed to be the rate parameter to a Poisson distribution; so year-to-year variability in the number of cases could be modeled using this distribution. For the most part, this variability is ignored in this risk characterization because it represents a change of only about 5% around the estimated annual rate. Compared to the substantial uncertainty surrounding the effectiveness of FSIS inspection, this amount of variability is minor.

The true effectiveness at reducing human health risk of any newly established FSIS inspection of Siluriformes is unknown. This is because the baseline prevalance of both contamination and illness are uncertain, and the rate at which FSIS inspection would achieve its ultimate reductions is unknown as well. Consequently, the model incorporates substantial uncertainty about program effectiveness. A plausible range might be from more than 90% to less than 10% effectiveness, and so the risk assessment model includes an evaluation of possible effectiveness levels – 10%, 50% and 90% – to provide a range of predictions. Similarly, the model evaluates what the public health effect would be if the FSIS Siluriformes inspection program achieves peak effectiveness in 2, 5, 10 or 15 years following its implementation. Linear interpolation is used to predict the estimated illnesses avoided in the years prior to the designated timeframe to achieve peak effectiveness in a given scenario.

6.3.1 Poultry evidence

Although the risk assessment model includes uncertainty about the effectiveness of FSIS inspection as a range between 10% and 90%, evidence from before and after implementation of the FSIS HACCP regulation provides some indication of a midpoint between these extremes. For example, the 1994-95 nationwide broiler chicken microbiological baseline study found 20% of 1,297 poultry carcasses *Salmonella*-positive. That study was repeated in 1999-2000 and found 8.7% of 1,225 poultry carcasses *Salmonella*-positive. In 2007-2008, FSIS again completed a nationwide baseline study of poultry carcasses and found approximately 7.5% (volume-weighted) of 3,275 samples *Salmonella*-positive[36].

The trend in *Salmonella* prevalence among poultry carcasses does not directly demonstrate the effectiveness of the HACCP regulation; too many factors might influence *Salmonella* occurrence among carcasses to attribute the trend solely to FSIS inspection activities. Nevertheless, this trend provides an empirical estimate of how FSIS inspection might influence *Salmonella* occurrence among FSIS-regulated products. This trend – if fully attributed to FSIS' inspection program – implies that *Salmonella* prevalence might decrease (i.e., by $\left(1-\frac{8.7\%}{20\%}\right)=56.5\%$ or $\left(1-\frac{7.5\%}{20\%}\right)=62.5\%$) following implementation of FSIS' Siluriformes inspection program.

We note, however, that under FSIS HACCP inspection, *Salmonella* prevalence has varied over time within meat and poultry product classes and among classes and establishment sizes. In a minority of cases, *Salmonella* prevalence has proved resistant to improvement. Therefore, the difference in *Salmonella* prevalence witnessed between the 1994-95 and 2007-08 microbiological baselines for broilers may not be indicative of the future trends in the microbiological quality of catfish, and substantial time and adaptations may be required before improvements are realized.

6.4 Program effectiveness estimates

Estimates of the potential effectiveness of FSIS Siluriformes program are presented relative to the estimated baseline number of salmonellosis cases potentially associated with catfish (of the order Siluriformes) consumption. As discussed previously, predicted program effectiveness depends upon the number of baseline *Salmonella* illnessses, the peak effectiveness rate of an FSIS Siluriformes inspection program, and the timeframe required to achieve peak effectiveness.

It is important to note that estimates of the number of baseline *Salmonella* illnesses attributable to these fish differ depending on whether considering all Siluriformes or specifially Ictaluridae. The number of baseline *Salmonella* illnesses

[36] See http://www.fsis.usda.gov/Science/Baseline_Data/index.asp for all baseline studies

estimated is higher (2,308 illnesses per year) for Siluriformes, and lower (1,764 illnesses per year) for Ictaluridae. Because these baseline *Salmonella* illnesses are assumed to be Poisson distributed, the risk assessment estimates (Table 12) also include 5th and 95th percentiles.

Table 12. Estimate of baseline *Salmonella* illnesses per year.[a]

		Confidence Interval	
Catfish Definition	Mean	5th	95th
Siluriformes	2,308	2229	2387
Ictaluridae	1,764	1695	1833

[a] Estimates of the mean are derived using the process model and the confidence intervals are generated from an assumed Poisson distribution.

Substantial uncertainty remains about the level of peak effectiveness that could be achieved by an FSIS inspection program for Siluriformes. In theory, FSIS inspection of Siluriformes could be completely effective (100% peak effectiveness) at reducing salmonellosis cases assocated with the consumption of catfish (of the order Siluriformes), or, FSIS inspection could be totally ineffective (0% peak effectiveness). Model results are summarized for three plausible effectiveness levels (i.e., 10%, 50%, and 90%).

Additional uncertainty exists about the number of years required to achieve peak effectiveness. The risk assessment assumes that the soonest that FSIS' Siluriformes inspection program could achieve peak effectiveness could be 2 years (therefore the 3rd year would be the first year of inspection under peak effectiveness). At the other extreme, it is assumed that an FSIS Siluriformes inspection program could take 15 or more years to achieve peak effectiveness. Other plausible scenarios modeled include a 5-year timeframe and a 10-year timeframe.

6.4.1 Analysis of Siluriformes

Figure 6 shows several aspects of the the uncertainty about the estimated peak effectiveness of an FSIS regulation in predicting the annual number of *Salmonella* illnesses avoided, using the Siluriformes definition of catfish. This graph assumes a 5-

year timeframe for reaching an uncertain peak effectiveness. Note that the relative estimanted number of illnesses avoided across 10 years of an FSIS Siluriformes inspection program is directly related to the assumption about the timing of peak effectiveness.

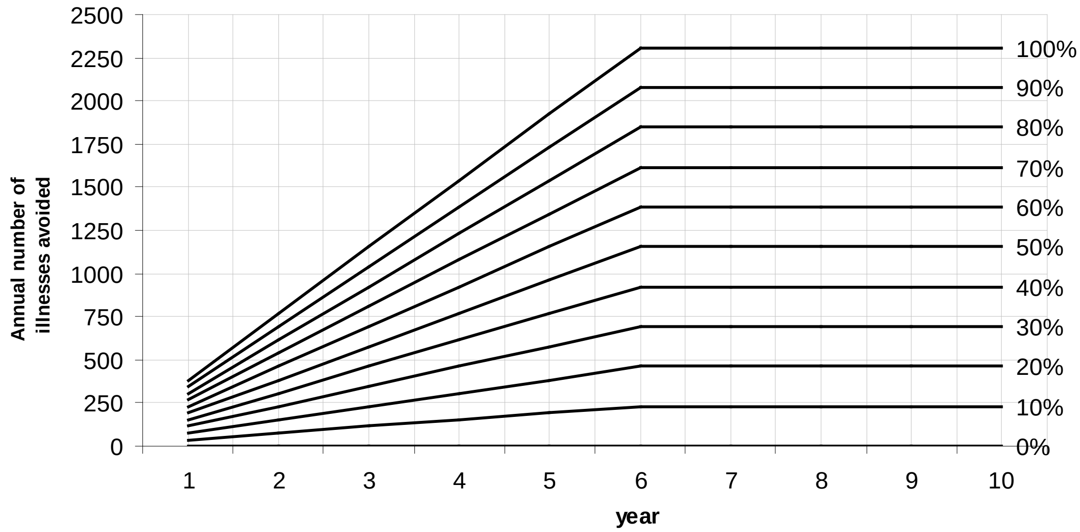

Figure 6. Uncertainty in the potential effectiveness of regulation on the annual number of *Salmonella* illnesses avoided over 10-yrs following FSIS regulation of Siluriformes. These values assume a 5-yr timeframe and the Siluriformes definition of catfish.

Tables 13 through 15 show the number of *Salmonella* illnesses avoided each year over a 10-year planning horizon for 10%, 50%, and 90% peak effectiveness, assuming a 2, 10 or 15-year timeframe for achieving peak effectiveness.

Estimated illnesses avoided are then projected for each of 10-years following policy implementation. If the peak effectiveness of an FSIS Siluriformes inspection progam is assumed to be a 50% decline in salmonellosis cases related to these fish, then a comparison of Tables 13 through 15 shows that predicted *Salmonella* illnesses from estimated contmination of these fish avoided in the first year ranges from a low of 72 (assuming a 15-year timeframe to achieve peak effectiveness) to a high of 384 (assuming a 2-year timeframe to achieve peak effectiveness).

If the peak effectiveness of an FSIS Siluriformes inspection progam is assumed to be at 90%, then comparing Tables 13 through 15 shows predicted *Salmonella* illnesses from these fish avoided in the first year ranges from a low of 129 (assuming a 15-year timeframe to achieve peak effectiveness) to a high of 692 (assuming a 2-year timeframe to achieve peak effectiveness).

In this analysis, the risk asssessment model is used to project the estimated number of *Salmonella* illnesses associated with these fish that might be avoided over a 10-year period to allow for the calculation of the discounted value of human illnessess avoided for a 10-year benefit-cost analysis. It is worth noting that the longer timeframes require more time to achieve higher predicted illnesses avoided. For example, using the 15-year timeframe and assuming peak effectiveness at 90%, the risk assessment model estimates 1,298 *Salmonella* illnesses avoided in the tenth year. In a valuation calculation of these human illnesses in the present, they must be discounted for 10 years. The shorter the timeframe required to achieve peak effectiveness, the smaller the gap between the estimated number of *Salmonella* illnesses associated with these fish avoided in the near-years of the planning horizon and the estimated number of illnesses avoided in the out-years of the planning horizon. This has potentially important implications for benefit-cost analysis.

Table 13. Estimated Number of *Salmonella* illnesses avoided due to FSIS regulation of Siluriformes assuming a 2-year to effectiveness timeframe.

	90% Effectiveness			50% Effectiveness			10% Effectiveness		
		C.I. (Percentile)			C.I. (Percentile)			C.I. (Percentile)	
Year	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th
1	692	649	735	384	352	416	76	62	90
2	1,384	1,323	1,445	769	723	815	153	133	173
3	2,077	2,002	2,152	1,154	1,098	1,210	230	205	255
4	2,077	2,002	2152	1,154	1,098	1,210	230	205	255
5	2,077	2,002	2,152	1,154	1,098	1,210	230	205	255
6	2,077	2,002	2,152	1,154	1,098	1,210	230	205	255
7	2,077	2,002	2,152	1,154	1,098	1,210	230	205	255
8	2,077	2,002	2,152	1,154	1,098	1,210	230	205	255
9	2,077	2,002	2,152	1,154	1,098	1,210	230	205	255
10	2,077	2,002	2,152	1,154	1,098	1,210	230	205	255

Abbreviation: C.I., Confidence Interval.

Table 14. Estimated Number of *Salmonella* illnesses avoided due to FSIS regulation of Siluriformes assuming a 10-year to effectiveness timeframe.

	90% Effectiveness			50% Effectiveness			10% Effectiveness		
		C.I. (Percentile)			C.I. (Percentile)			C.I. (Percentile)	
Year	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th
1	188	165	211	104	87	121	20	13	28
2	377	345	409	209	185	233	41	31	52
3	566	527	605	314	285	343	62	49	75
4	755	710	800	419	385	453	83	68	98
5	944	893	995	524	486	562	104	87	121
6	1,133	1,078	1,188	629	588	670	125	107	143
7	1,321	1,261	1,381	734	689	779	146	126	166
8	1,510	1,446	1,574	839	791	887	167	146	188
9	1,699	1,631	1,767	944	893	995	188	165	211
10	1,888	1,817	1,959	1,049	996	1,102	209	185	233

Abbreviation: C.I., Confidence Interval.

Table 15. Estimated Number of *Salmonella* illnesses avoided due to FSIS regulation of Siluriformes assuming a 15-year to effectiveness timeframe.

	90% Effectiveness			50% Effectiveness			10% Effectiveness		
		C.I. (Percentile)			C.I. (Percentile)			C.I. (Percentile)	
Year	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th
1	129	110	148	72	58	86	14	8	20
2	259	233	285	144	124	164	28	20	37
3	389	357	421	216	192	240	43	33	54
4	519	482	556	288	260	316	57	45	70
5	649	607	691	360	329	391	72	58	86
6	778	732	824	432	398	466	86	71	101
7	908	858	958	504	467	541	100	84	116
8	1,038	985	1,091	577	537	617	115	97	133
9	1,168	1,112	1,224	649	607	691	129	110	148
10	1,298	1,239	1,357	721	677	765	144	124	164

Abbreviation: C.I., Confidence Interval.

6.4.2 Analysis of Ictaluridae[37]

Figure 7 shows the uncertainty about the peak effectiveness of FSIS regulation in predicting the estimated annual number of *Salmonella* illnesses avoided if FSIS were to specfically inspect Ictaluridae instead of Siluriformes. This graph assumes a 5-year timeframe for reaching an uncertain peak effectiveness.

Tables 16 through 18 show the estmated number of *Salmonella* illnesses avoided each year over a 10-year planning horizon for 10%, 50%, and 90% peak effectiveness assuming a 2, 10, and 15-year timeframe for achieving the peak effectiveness. If the peak effectiveness of an FSIS Ictaluridae inspection progam were assumed to be a 50% decline in *Salmonella* illnesses related to Ictaluridae, then a comparison of Tables 16 through 18 shows that predicted *Salmonella* illnesses from these fish avoided in the first year ranges

[37] This section was developed and posted to FSIS' website before the February 7, 2014 Agricultural Act of 2014 (Pub. L. 113-79, Sec. 12106), known as the 2014 Farm Bill, amended Section 1(w) of the FMIA to remove the phrase "catfish, as defined by the Secretary," and replace it with "all fish of the order Siluriformes," thus including these fish among the amenable species (21 U.S.C. 601(w)(2)). This section has been included in this risk assessment for completeness and consistency with the previous version of the risk assessment, but represent a definition of catfish that is narrower than the Siluriformes that FSIS will inspect.

from a low of 55 (assuming a 15-year timeframe to achieve peak effectiveness) to a high of 294 (assuming a 2-year timeframe to achieve peak effectiveness).

If the peak effectiveness of an FSIS inspection progam that were specific to Ictaluridae is assumed to be 90%, then a comparison of Tables 16 through 18 shows that estimated illnesses avoided in the first year range from a low of 99 (assuming a 15 timeframe to achieve peak effectiveness) to a high of 529 (assuming a 2-year timeframe to achieve peak effectiveness).

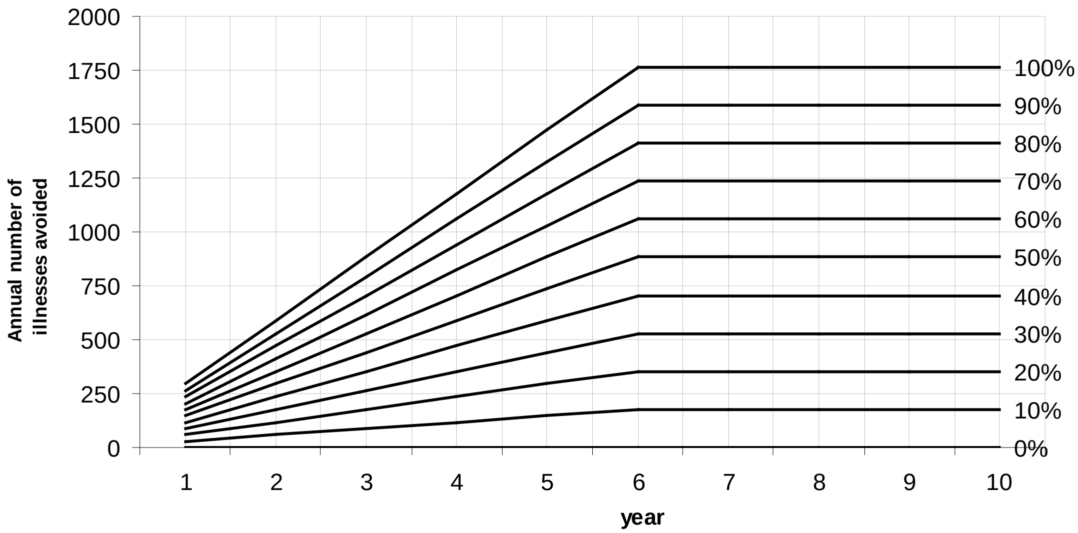

Figure 7. Uncertainty in the potential effectiveness of regulation on the annual number of *Salmonella* illnesses avoided over 10-yrs following FSIS regulation if it were specific to Ictaluridae. These values assume a 5-yr timeframe and that there were an FSIS inspection system specifically for Ictaluridae.

Table 16. Estimated Number of *Salmonella* illnesses avoided if FSIS were to specifically regulate Ictaluridae and assuming a 2-year to effectiveness timeframe.

	90% Effectiveness			50% Effectiveness			10% Effectiveness		
		C.I. (Percentile)			C.I. (Percentile)			C.I. (Percentile)	
Year	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th
1	529	491	567	294	266	322	58	46	71
2	1,058	1,004	1112	588	548	628	117	99	135
3	1,587	1,521	1653	882	833	931	176	154	198
4	1,587	1,521	1653	882	833	931	176	154	198
5	1,587	1,521	1653	882	833	931	176	154	198
6	1,587	1,521	1653	882	833	931	176	154	198
7	1,587	1,521	1653	882	833	931	176	154	198
8	1,587	1,521	1653	882	833	931	176	154	198
9	1,587	1,521	1653	882	833	931	176	154	198
10	1,587	1,521	1653	882	833	931	176	154	198

Abbreviation: C.I., Confidence Interval.

Table 17. Estimated Number of *Salmonella* illnesses avoided if FSIS were to specifically regulate Ictaluridae and assuming a 10-year to effectiveness timeframe.

	90% Effectiveness			50% Effectiveness			10% Effectiveness		
		C.I. (Percentile)			C.I. (Percentile)			C.I. (Percentile)	
Year	Mean	5th	95th	Mean	5th	95th	Mean	5th	95th
1	144	124	164	80	65	95	16	10	23
2	288	260	316	160	139	181	32	23	42
3	432	398	466	240	215	265	48	37	60
4	577	537	617	320	291	349	64	51	77
5	721	677	765	400	367	433	80	65	95
6	865	817	913	481	445	517	96	80	112
7	1,010	958	1,062	561	522	600	112	95	129
8	1,154	1,098	1,210	641	599	683	128	109	147
9	1,298	1,239	1,357	721	677	765	144	124	164
10	1,443	1,381	1,505	801	754	848	160	139	181

Abbreviation: C.I., Confidence Interval.

Table 18. Estimated Number of *Salmonella* illnesses avoided if FSIS were to specifically regulate Ictaluridae and assuming a 15-year to effectiveness timeframe.

	90% Effectiveness			**50% Effectiveness**			**10% Effectiveness**		
		C.I. (Percentile)			**C.I. (Percentile)**			**C.I. (Percentile)**	
Year	**Mean**	**5th**	**95th**	**Mean**	**5th**	**95th**	**Mean**	**5th**	**95th**
1	99	83	115	55	43	67	11	6	17
2	198	175	221	110	93	127	22	15	30
3	297	269	325	165	144	186	33	24	43
4	396	363	429	220	196	244	44	33	55
5	496	459	533	275	248	302	55	43	67
6	595	555	635	330	300	360	66	53	79
7	694	651	737	385	353	417	77	63	91
8	793	747	839	441	406	476	88	73	103
9	893	844	942	496	459	533	99	83	115
10	992	940	1044	551	512	590	110	93	127

Abbreviation: C.I., Confidence Interval.

6.5 Sensitivity of default illnesses estimates to changes in some model inputs

A limited sensitivity analysis was completed on inputs to the risk assessment model to inform the uncertainty analysis and to test the sensitivity of certain modeling assumptions. This sensitivity analysis was conducted on the baseline number of *Salmonella* illnesses.

Below is a description of the procedures used to evaluate the influence of various risk assessment model parameters on public health estimates (i.e., the sensitivity of model variables).

Elasticities, Є, are calculated for every sensitivity test based on the following formula:

Є = %Δ in output / (%Δ in input)

where %Δ is read “percent change”. The greater the absolute value of the elasticity, the more effect a change in a model input can be expected to have on the outputs of this risk assessment model.

For the sensitivity procedure, the model was run for 3 million *Salmonella*-contaminated servings and the output was collected (YBASE). A change to an input parameter was initiated in the model, then the model was re-run for 3 million *Salmonella*-contaminated servings and the output was again collected (YSHOCK). To assure consistency of comparisons, the same starting seed value was used in all baseline and sensitivity scenario runs of the model.

The %Δ in output is calculated as:

$$\%\Delta \textit{ in output} = (YSHOCK - YBASE) / YBASE$$

Similarly, the %Δ *in input* values could be determined. In practice these were entered as exogenous pre-run changes to one input variable at a time in the model code.

This model uses several input parameters. The advantage of elasticity-based sensitivity analysis is that the analyst can compare and contrast sensitivities across all inputs using a common metric.

6.5.1 Prevalence

Both import and domestic prevalence assumptions were tested by increasing the default inputs by 10%.

6.5.2 Growth

One sensitivity scenario tested *Salmonella* growth assumptions in post- process carcasses by increasing the most likely parameter of the log growth *Pert* distribution by 100%. This large change was needed for this sensitivity scenario because very few servings experience growth.

6.5.3 Cooking practices

Pert distributions were used to model cooking times and temperatures for baked or fried servings. Sensitivities to cooking time and cooking temperature were tested separately for baking and frying. The most likely cooking times were adjusted by 10%. The most likely cooking temperatures were adjusted by 8.5% because a 10% increase would exceed the maximum parameter in the *Pert* distribution.

Additional sensitivity scenarios tested model assumptions about fraction of catfish (of the order Siluriformes) meals baked and the fraction of servings breaded. Both of these scenarios assumed 10% increases in the respective input parameter.

6.5.4 Serving Size

The sensitivity of the model's output to serving size was modeled by multiplying random draws for the non-parametric serving size distribution (documented elsewhere in this report) by a factor of 1.1 – thus achieving a 10% increase in serving size.

Additionally, sensitivity analyses were developed on assumptions about the reduction in serving size due to breading. These scenarios involved increasing the minimum and maximum reductions in serving size from breading by 10%.

6.5.5 Dose-Response

The beta-Poisson dose response function for *Salmonella* was tested for sensitivity by analyzing small changes to the individual parameters of the beta-Poisson. Both the α and β parameters were adjusted by 10%.

6.5.6 Assumptions about extrapolating from poultry to Siluriformes

Two assumptions regarding extrapolation of poultry to fish carcasses were tested. A 10% change to the assumption about the average weight of a poultry carcass in a rinse bag (used to estimate *Salmonella* concentration) was tested. Also, this risk assessment includes an evaluation of model assumptions about the effect of skin removal on overall carcass contamination by adjusting that value by 10%.

6.5.7 Sensitivity analysis findings

Sensitivity scenario results can be loosely grouped into 3 categories (|Є|>1, |Є|~1, |Є|<<1). By far, the most sensitive model inputs are the assumptions about cooking ((|Є|>1). Frying parameters seem much more sensitive than baking parameters. Cooking temperature also seems more sensitive than cooking time. Elasticities for a second category of input parameters are close to one; therefore a proportional change in *Salmonella* illnesses results for a given change in input values. Those include the α and β parameters of the dose response function, serving size, underlying assumptions about poultry contamination (effect of skin removal, and weight of chicken carcass in the rinse solution used to extrapolate contamination levels) and domestic prevalence. All other parameters fall into a third category of inputs having elasticities less than one. Results of the sensitivity analysis on all relevant *Salmonella* input variables are shown in Figure 8.

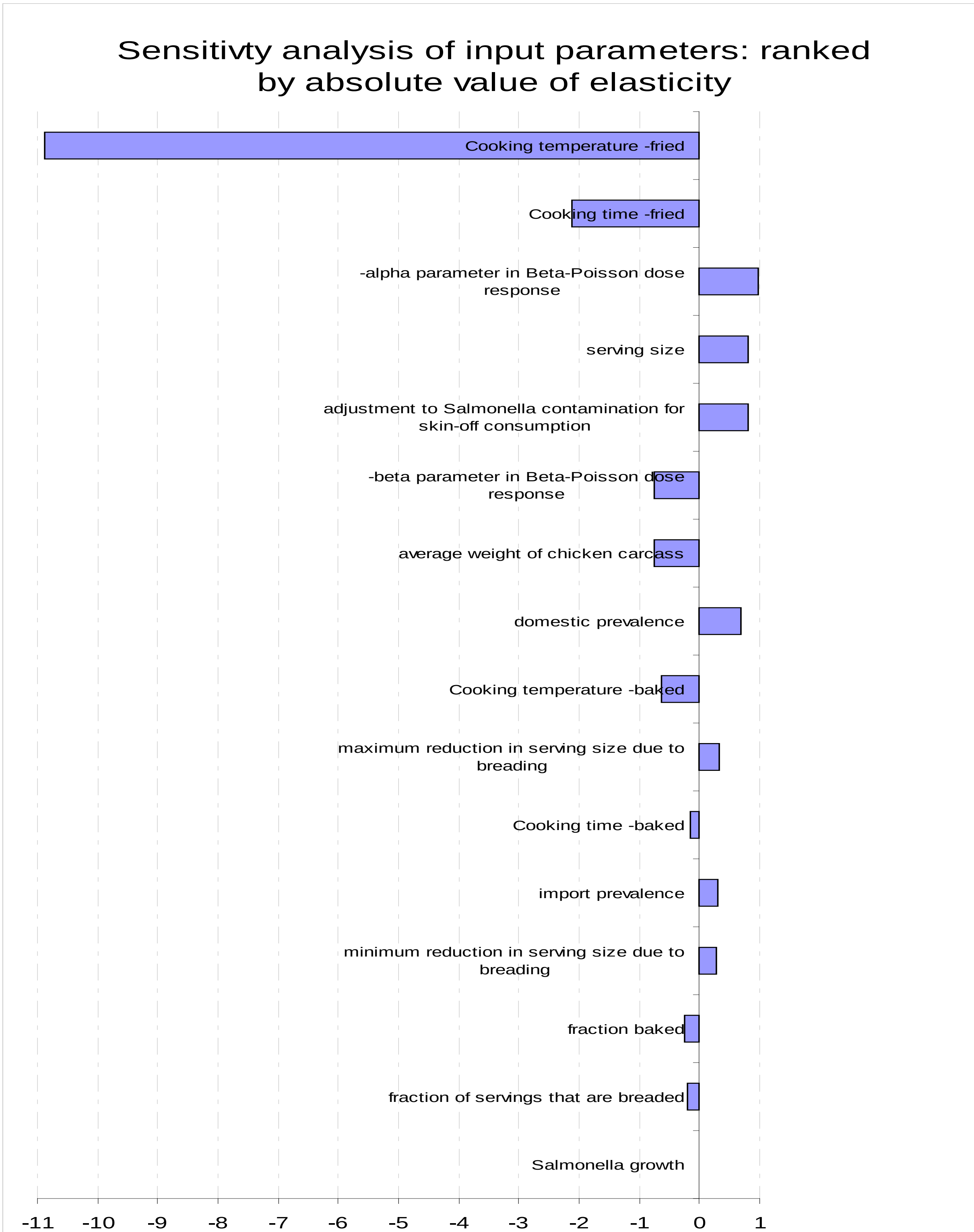

Figure 8. Tornado diagram describing the elasticity of the model's annual illness estimates to various model inputs. The x-axis is in elasticity units.

6.6 Uncertainty scenario analyses

The purpose of uncertainty analysis is to examine the effect of some of the default estimates on the annual number of human *salmonellosis* cases estimated from catfish (of the order Siluriformes) consumption. Although this risk assessment uses a simple model, the default input values were usually based on assumptions or very limited data. Uncertainty analysis can also highlight the need for specific data to improve a risk assessment's estimates. Both these objectives are treated in a mostly qualitative manner in this section.

To evaluate the uncertainty in some model estimates, the risk assessment estimates annual numbers of illnesses for various model inputs using the Siluriformes definition of catfish. For various model inputs, potential lower and upper bound values are used (Table 19). In some cases, the potential lower and upper bounds are determined from statistical confidence limits; while in other cases the settings are determined based on judgments of the data underlying the default assumptions. For example, there is some evidence suggesting an upward trend in imported products (USDA-NASS, 2009). In addition, there is some evidence to suggest *Salmonella* prevalence might be larger than 2% for some share of imported product (Broughton and Walker 2009)[38]. Given this limited evidence, an upper bound scenario for prevalence adjusts the prevalence among imports and increases the share of imports. Nevertheless, a similar effect could have been modeled by simply increasing prevalence among domestic product. Alternatively, a lower bound scenario for prevalence assumes that *Salmonella* prevalence among all catfish is closer to 1% based on limited sampling at retail (Pao et al. 2008).

The default growth, breading effect, and post-processing concentration modeling assumptions were considered already to be near lower bound settings, so only upper bound scenarios were developed for these inputs. Potential upper and lower bound settings for cooking effectiveness were established by adjusting cooking times such that

[38] Nevertheless, there is also historic evidence that *Salmonella* prevalence among domestic catfish may also be higher than 2% (Wyatt et al. 1979).

frying became equivalent to baking (lower bound) or baking became equivalent to frying (upper bound).

Each change (lower and upper) was simulated to estimate the annual number of illnesses and the change from the default model estimate was noted. For each potential upper and lower bound value, the inputs were sorted from smallest change to largest change. Scenarios that progressively combined more changes were simulated next, so that the incremental effect on estimated illnesses could be examined.

This approach progressively assumes that uncertainty about model inputs is perfectly correlated. In other words, if the true value for one input is its lower bound, then the true values for one, two, three, etc. other inputs is/are also their lower bounds. Such an approach predicts extreme boundaries because any assumption about uncertainties not being perfectly correlated will demonstrate less change in the model estimates than shown. Nevertheless, the progressive inclusion of multiple inputs into scenarios illustrates the range of uncertainty about the lower and upper bounds. As opposed to only providing the most extreme result (setting all inputs to their potential lower/upper bounds), we assume the range for these boundaries is qualitatively useful for decision-makers.

Table 19. An outline of potential lower and upper bound values for various model inputs is shown. Symbols are used to identify changes in Figure x and y.

Input name	Symbol	Lower Bound Scenario	Upper Bound Scenario
Serving size	*S*	Use lower 95% confidence limit for quantiles of empiric distribution	Use upper 95% confidence limits for quantiles of empiric distribution
Dose-response parameters	*DR*	Use lower 95% confidence limit alpha and beta parameters from WHO/FAO, 2002; α =0.094, β =43.75	Use upper 95% confidence limit alpha and beta parameters from WHO/FAO, 2002; α =0.1817, β =56.39
Skinless effect adjustment	*K*	Reduce poultry contamination data by 0.9 logs	Reduce poultry contamination data by 0.5 logs
Prevalence of contaminated product	*P*	Reduce prevalence to 1% for both domestic and imported product	Increase prevalence for imported product to 4% and increase import share to 40%
Cooking effectiveness	*C*	Frying time distribution set equal to baking time distribution	Baking time distribution set equal to frying time distribution
Growth effect	*G*	No change	Set probability of growth to 0.2%; most likely log growth=0.40; maximum log growth=1.5
Breading effect	*B*	No change	Minimum adjustment=0.85; maximum=0.95 (i.e., breading constitutes 5% to 15% of serving size)
Post-processing concentration	*X*	No change	Truncate *Salmonella* concentration distribution at 0.03 *Salmonella* per gram, but re-distribute lower values randomly to values above threshold

The analysis completed for the potential lower bound scenario illustrates that the estimated annual *Salmonella* illnesses associated with Siluriformes may range from 1,942 to 100 (relative to a default of 2,308) depending on how many inputs assume the potential lower bound values (Figure 9). Although other combinations are possible (e.g., $S+K$ or

$S+P+C$), this approach is one system for examining how the model's estimate is reduced as more of its inputs are set at their lower bounds.

As the graph progressively includes another uncertain input set to its potential lower bound, the estimated annual illnesses decreases. The pattern suggests a weak exponential-like decline as each input limits the amount of exposure (or response to exposure) among fish servings. Nevertheless, the incremental effect of improved cooking (C) at the end of the progression is limited in Figure 9 relative to its effect when all other inputs are set at their default values. If the cooking inputs for the lower bound scenario are the only change to the default model, then estimated annual illnesses are 524 (i.e., the incremental effect of lower bound cooking adjustment eliminates 1784 illnesses relative to the default estimate). This effect alone is nearly equivalent to the effect estimated by the $S+DR+K+P$ combined scenario. But, when the cooking change is modeled in combination with all other changes, its influence on illnesses is modulated because fewer contaminated servings with fewer organisms (and a lower probability of illness) are available in the model to be affected by the improved cooking effectiveness.

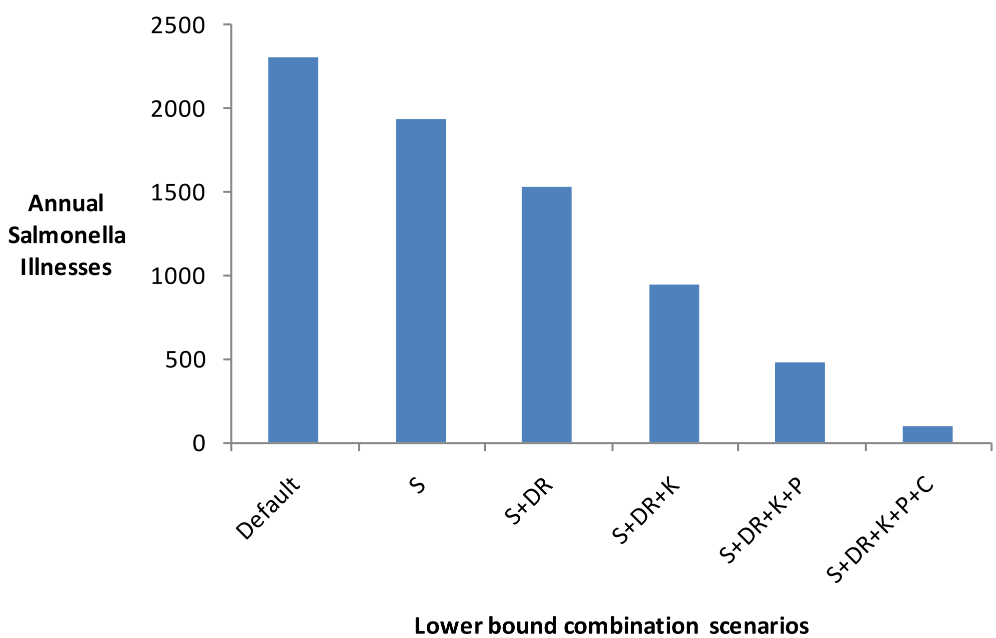

Figure 9. Cumulative reduction in the estimated number of illnesses for combined potential lower bound scenarios.

The analysis completed for the potential upper bound scenario illustrates that the estimated annual illnesses may range from 2,397 to 16,000 (relative to a default of 2,308) depending on how many inputs assume their potential upper bound values (Figure 10). The trend in this graph suggests an exponential-like increase in estimated annual illnesses as more inputs are set to their upper bounds.

The largest increase in estimated annual illnesses occurs when the *Salmonella* concentration data (derived from poultry) is truncated differently. The default assumption is that concentrations less than 0.003 *Salmonella* per gram are equal to 0.003. This assumption creates a high frequency of contaminated carcasses with exactly 0.003 *Salmonella* per gram. In the potential upper bound scenario, any value less than 0.003/g is randomly redistributed to values above the threshold. This approach is conceptually similar to zero-truncated discrete distributions in which values of zero are removed from the distribution and the probabilities for remaining feasible values are adjusted to sum to one (Klugman 2004).

For example, the default model estimates a mean (mode) of 0.13 (0.003) *Salmonella*/g on contaminated carcasses. The potential upper bound scenario estimates a mean (mode) of 0.35 (0.016) *Salmonella*/g (i.e., nearly a 3-fold increase in average concentration). This increase in concentration translates into a nearly proportional increase in annual illnesses (i.e., from 2308 to 6318 cases per year).

Although the truncation method is a modeling assumption, the default model creates a contamination distribution that is consistent with conventional wisdom. It is generally reasonable to assume that the frequency of contamination levels decreases with increasing contamination levels (i.e., that contamination frequency is a monotonically decreasing function of contamination). Nevertheless, there are no contamination data currently available for testing this assumption; once FSIS inspection begins, this uncertainty can be addressed by collecting Siluriformes samples and enumerating *Salmonella* levels on positive samples.

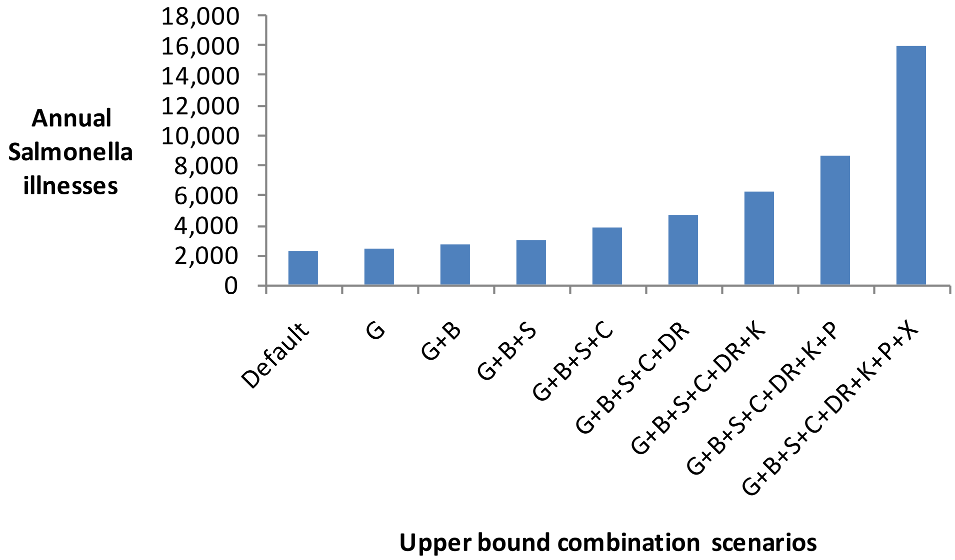

Figure 10. Cumulative increase in the estimated number of illnesses for combined potential upper bound scenarios.

A comparison of these potential upper and lower bound analyses with the inferences drawn from public health surveillance data suggests that the potential lower bound estimates are similar for both (i.e., 100 versus 280 estimated from public health data), but the potential upper bound estimates from this boundary analysis trend toward substantially larger annual illnesses (e.g., 16,000) than those estimated from public health data (6,700). Because it is assumed that a large number of annual illnesses is inconsistent with current public health surveillance data (i.e., if Siluriformes were truly responsible for tens of thousands of *Salmonella* illnesses each year, it is expected that there would be more evidence of this food source based on epidemiological data), the risk assessment model is designed to examine the scenario from the upper bound analysis that most closely approximates the 6,700 annual illnesses estimated from the analysis of public health data. This scenario, $G+B+S+C+DR+K$, estimates 6,193 annual illnesses. The risk assessment model is used to examine the effect of FSIS inspection on this scenario and the $S+DR+K+P+C$ lower bound scenario.

Recalling that the effect of FSIS regulation on Siluriformes is dependent on the assumption about the peak effectiveness of the regulation and on the timeframe required to achieve peak effectiveness, incorporating additional uncertainty with respect to baseline illness projections further complicates presentation of these results. For illustrative purposes, assume a 50% peak effectiveness of FSIS inspection and a 5-year timeframe for achieving that level of peak effectiveness (Table 20). Given these assumptions, Table 20 shows the number of *Salmonella* illnesses avoided for both the lower bound scenario ($S+DR+K+P+C$ lower) and the plausible upper bound scenario ($G+B+S+C+DR+K$ upper). Annual illnesses avoided ranges from a low of 8 (potential lower bound scenario) to a high of 516 (potential upper bound scenario) in the first year of the program. Since these average estimates are again Poisson distributed, confidence intervals are placed around these estimates of *Salmonella* illnesses avoided per year. Similar to the estimates using the default parameter values, these estimates will vary by year depending on the assumption about timeframe and peak effectiveness of FSIS regulation.

Table 20. Estimated Number of *Salmonella* illnesses avoided by FSIS regulation of Siluriformes Assuming a 5-year Timeframe and 50% Effectiveness of FSIS inspection

	Lower Bound Scenario[1]			Upper Bound Scenario[2]		
		C.I. (Percentile)			C.I. (Percentile)	
Year	Mean	95th	5th	Mean	95th	5th
1	8	13	4	516	553	479
2	16	23	10	1032	1085	979
3	25	33	17	1548	1613	1483
4	33	43	24	2064	2139	1989
5	42	53	32	2580	2664	2496
6	50	62	39	3096	3188	3004
7	50	62	39	3096	3188	3004
8	50	62	39	3096	3188	3004
9	50	62	39	3096	3188	3004
10	50	62	39	3096	3188	3004

Abbreviation: C.I., Confidence Interval.

[1] Combines lower bound assumptions for serving size, dose response parameter values, skinless effect on fillet contamination levels, *Salmonella* prevalence, and cooking affect.

[2] Combines upper bound assumptions for growth, breading affect, serving size, cooking effect, dose response parameter values, skinless effect on fillet contamination levels.

7. Summary

This risk assessment was completed to inform regulatory rule-making for establishing an FSIS Siluriformes inspection program. This risk assessment also considered two definitions for catfish – the definition of the order Siluriformes and the subset of the family Ictaluridae. As a baseline, i.e. prior to the establishment of an FSIS Siluriformes inspection program, this risk assessment estimates an average of 2,308 (Confidence Intervals: 5^{th}, 2,229; 95^{th}, 2,387) *Salmonella* illnesses per year in the U.S. associated with the consumption of Siluriformes. The assessment estimates an average of 1,764 illnesses associated with the consumption of Ictaluridae. These estimates are not inconsistent with those that might be projected by extrapolating current CDC epidmiological data (i.e., outbreak data). Based on the total number of servings of these fish consumed in the U.S., regardless of the definition, the default probability of *Salmonella* illness per serving of such fish is estimated to be 1.5×10^{-6}. This probability incorporates the prevalence of *Salmonella*-contaminated servings and suggests salmonellosis from consuming a serving of such fish is an uncommon event.

There is substantial uncertainty regarding the actual effectiveness of a future FSIS Siluriformes inpsection program. The actual effectiveness of FSIS' Siluriformes inspection program in reducing the prevalence of *Salmonella*-contaminated Siluriformes will directly influence the size of the likely benefits of such a program. To illustrate, this risk assessment predicts that if FSIS has a Siluriformes inspection program fully operational within a two year timeframe, then between 230 and 2,077 salmonellosis cases might be prevented per year, depending on whether the program is 10% or 90% effective.

Finally, the range of risk estimates depends on uncertainty about the model and the model inputs (e.g., data quality and assumptions). Uncertainty about these inputs translates into substantial uncertainty about the baseline estimates of the annual number of human salmonellosis cases attributable to the consumption of catfish (of the order Siluriformes). Consideration of potential lower and upper bound model scenarios suggest plausible model estimates between 100 and 6,200 salmonellosis cases associated with Siluriformes per year. Given these public health estimates, this risk assessment estimates that between 50 and about 3,100 salmonellosis cases might be prevented if an FSIS inspection program is 50% effective within a 5-year timeframe. If only Ictaluridae are considered, then between 38 and about 2,353 cases might be prevented each year.

Given current uncertainties about the effectiveness of this future program and limited contamination data for Siluriformes, this food safety risk assessment provides estimates of potential public health benefits of an FSIS Siluriformes inspection program.

8. References

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Addendum

Following the passage of the Agricultural Act of 2014 (Pub. L. 113-79, Sec. 12106), FSIS conducted a literature search to identify any research published since FSIS developed this risk assessment and searched the Centers for Disease Control and Prevent (CDC) outbreak database to determine whether any new research or outbreak information would affect the previously conducted risk assessment.

The National Library of Medicine's PubMed Database was searched using the key word Siluriformes for articles published since 2008. That search yielded about 1,200 articles related to Siluriformes. The abstracts from those articles were reviewed to identify any articles which could affect the hazard identification or the risk assessment. A number of publications discussed the concentrations of different environment contaminants in wild catfish, and in some cases farm-raised catfish, from locations around the globe. Most of those contaminants, with the exception of polycyclic aromatic hydrocarbons (PAHs) and polybrominated diphenyl ethers (PBDEs), are already discussed in Chapter 2 of this report and did not contain information that would substantively change the hazard identification or risk assessment. Potentially relevant articles are discussed below.

Two articles that evaluated chemicals not previously discussed in the hazard identification are summarized here. Squadrone et al. (2014) analyzed European catfish (*Silurus glanis*) samples from the upper Po River basin for the levels of nine PAHs (naphthalene, acenaphthene, fluorene, phenanthrene, anthracene, pyrene, benz[a]anthracene, chrysene, and benz[a]pyrene) and detected PAHs in a number of the muscle samples. Staskal et al. (2008) analyzed wild-caught and farm-raised catfish samples from southern Mississippi for 43 PBDEs. PBDE concentrations were significantly higher in wild-caught (median concentration of 2.7 ng/g wet weight) than farm-raised (median concentration of 0.5 ng/g wet weight) catfish samples. The authors estimated exposures from daily consumption, and concluded that the health risks from PBDEs in wild-caught or farm-raised catfish are substantially lower than risk levels "generally considered to be at the U.S. EPA minimum concern level."

There were a number of studies that analyzed US catfish, including farm-raised and commercially available catfish samples. Scott et al. (2009) analyzed the concentrations of “17 laterally substituted PCDD/Fs, 12 dioxin-like PCBs, and 97 non-dioxin-like PCBs” in wild-caught and farm-raised catfish samples from southern Mississippi, and estimated the potential health effects from exposure through consumption of those fish. The authors found that the concentrations of the various chemicals were lower than seen in earlier studies, indicating that concentrations might be decreasing, and that the cancer risk from exposure to PCCDD/Fs and dioxin-like and non-dioxin-like PCBs in catfish is low (less than $27.0x10^{-6}$). Huwe and Archer (2013) summarized data from 202 catfish samples collected in 2009 under the USDA Pesticide Data Program and analyzed for PCDD, PCDF, PCB, and PBDE. PCDD/F TEQs and dl PCB TEQs ranged from 0.02–3.46 and 0.001–0.10 pg/g wet weight, respectively. The total TEQs had decreased from what had been seen in earlier studies. The patterns of contamination and levels indicated that the source of contamination might be from mineral clays used in catfish feed (Huwe and Archer, 2013).

Weintraub and Birmbahm (2008) identified catfish consumption as a potential source of elevated PCB levels in non-Hispanic Black anglers. The focus of that study on anglers who eat wild-caught catfish, however, makes it less relevant to this risk assessment.

Two studies focused on microbial contamination in catfish. Chen et al. (2010) examined catfish skins, intestines, fresh fillets and environmental samples from a catfish processing facility for the presence of *Listeria monocytogenes*. No contamination was isolated from the skin and intestine, but 76.7% of the chilled fresh catfish fillets and 43.3% of unchilled fillets were contaminated with *Listeria monocytogenes. Listeria monocytogenes* was also isolated from fish contact surfaces in the processing environment. The authors concluded that the processing environment might be the source of the contamination. Pao et al. (2008) tested fish samples purchased at retail markets in central Virginia or on the Internet for a number of microbes, including *Salmonella*, *E. coli* O157:H7, and *Listeria*. The researchers did not detect *E. coli* O157 or *Salmonella* in any of the samples. 22.2% and 25.0% of retail and Internet purchased samples, respectively, tested positive for *Listeria monocytogenes*.

A number of studies have isolated antimicrobial resistant bacteria in fish from aquaculture. Zhao et al. (2003) evaluated 187 Salmonella isolates from imported foods entering the United States collected by FDA, including fish and, specifically, catfish. Fifteen (8%) of the isolates exhibited some antimicrobial resistance, including three isolates from frozen catfish samples. Elsewhere, researchers investigating aquaculture-raised fish, including some catfish, have identified antibiotic resistant bacteria in a number of studies, including Salmonella species (Elhadi, 2014), E. coli (Ryu, 2011), and other bacteria (Akinbowale, 2006; Deng, 2014; Nagar, 2011; Petersen, 2002; and Resende, 2012). The relationship between antimicrobial chemicals in aquaculture and that antimicrobial resistance, however, has not been widely studied. Furthermore, Chen et al. (2010) did not identify antimicrobial resistant L. monocytogenes in catfish fillets or the catfish processing environment, but did note that "the presence of tet(M) gene in L. innocua raises the possibility of future acquisition of resistance by L. monocytogenes." Korsak et al. (2012) found a low prevalence of antimicrobial resistance in L. monocytogenes strains in Poland.

In addition, following the publication of the first version of this risk assessment, McCoy et al. (2011) published a review article summarizing the foodborne agents associated with the consumption of aquaculture catfish.

A brief summary of the full Agricultural Marketing Service (AMS) Pesticide Data Program (PDP) analysis of pesticide residues in domestic and imported catfish from 2008 to 2010 is included in Table A-1. Pesticides that were detected in more than five percent of samples were included in the table and are described in the following paragraphs. Table A-2 presents data on catfish and Pangasius sp from FDA's 2009–2013 seafood program.

Bifenthrin (or biphenthrin) is an EPA registered pyrethroid insecticide with no tolerance established in fish. Under CASRN 82657-04-3, the EPA has established an oral reference dose (RfD) of 0.015 mg/kg/day with tremors as the critical effect (dog). There is no carcinogenicity assessment.

Table A-1. Summary of the Agricultural Marketing Service's Pesticide Data Program (PDP) analysis of pesticide residues in Domestic and Imported Catfish: 2008 to 2010. [a]

	Positive (%)	Violative (%)	Number of Samples	LOD (ppb)	Maximum Concentration Detected (ppb)	Regulatory Level (ppb)	
						United States	Codex
Bifenthrin	15%	15%	1479	1.0	60	0	0
Chlorpyrifos	7%	7%	1479	1.0	40	0	0
DDD o,p'	13%	0%	1095	1.0-2.0	36	5,000	0
DDD p,p'	36%	0%	1095	1.0-2.0	138	5,000	0
DDE p,p'	75%	0%	1095	1.0-2.0	2310	5000	0
Diphenylamine (DPA)	11%	11%	1479	1.0-2.0	47	0	0
Diuron	7%	7%	1479	16	210	0	0
Endosulfan sulfate	7%	7%	1479	1.0	28	0	0
Toxaphene	8%	8%	1095	50	461	0	0

[a]Data are shown for pesticides detected in more than 5% of the catfish samples tested in the USDA AMS Pesticide Data Program from 2008–2010.
Abbreviations: LOD, Level of Detection; ppb, parts per billion.

Table A-2. Chemotherapeutics in FDA's Seafood Program (2009-2013): Catfish and other Pangasius sp Data.

Fiscal Year	Number of Samples Collected		Number of Analyses									Number of positive Samples (Drug Residue Detected; Country)
	Domestic	Import	CAM	NF	FQ	FFC	MG/ GV	QL	Sulfa Drugs	Stillbenes	MT	
2009	12	62	NT	NT	64	NT	61	15	NT	NT	NT	1 (GV; Vietnam)
2010	2	72	NT	1	70	NT	68	10	NT	NT	NT	2 (FQ; China, Vietnam)
2011	7	72	NT	1	67	NT	41	3	NT	NT	NT	0
2012	16	134	NT	54	102	NT	91	17	NT	6	4	1 (NF; Vietnam) 5 (FQ; China, Vietnam) 1 (MG; China)
2013	32	100	15	71	107	1	46	32	9	NT	15	0

Abbreviations: CAM, Chloramphenicol; FDA, US Food and Drug Administration; FFC, Florfenicol; FQ, Fluorquinolones; GV, Gentian Violet; MG, Malachite Green; MT, Methyltestosterone; NT, Nitrofurans; NT, Not Tested; QL, Quinolones.
Source: FDA.

Chlorpyrifos is an EPA registered insecticide. The chronic oral reference dose (RfD) is not given on the IRIS web site. The 2006 reregistration eligibility decision document for chlorpyrifos lists an oral RfD of 0.0003 mg/kg-bw/day, taking into account a NOEAL of 0.03 mg/kg-bw/day with an uncertainty factor of 100 and a Food Quality Protection Act factor of 10.

DDD and DDE are metabolites of DDT, which has been discussed earlier in the document.

Diphenylamine (DPA) is an EPA registered fungicide with no tolerance established in fish. Under CASRN 122-39-4, the EPA has established an oral reference dose (RfD) of 0.025 mg/kg/day with decreased body weight and increased liver and kidney weights as critical effects (dog). There is no carcinogenicity assessment.

Diuron, also known as DCMU, is an EPA registered herbicide with no tolerance established in fish. Under CASRN 330-54-1, the EPA has established an oral reference dose (RfD) of $2x10^{-3}$ mg/kg/day with abnormal pigments in blood as the critical effect (dog). There is no carcinogenicity assessment.

Endosulfan sulfate is a toxic oxidation product of endosulfan, an EPA registered organochlorine insecticide and acaricide that is currently being phased out by EPA. The last permitted use of endosulfan will expire July 31, 2016. There is no specific information in the EPA IRIS database on endosulfan sulfate, but endosulfan is listed with under CASRN 115-29-7. EPA has established an oral reference dose (RfD) of $6x10^{-3}$ mg/kg/day with reduced body weight gain in both males and females and increased incidence of marked progressive glomerulonephrosis and blood vessel aneurysms in males as the critical effects (rat).

Toxaphene is an insecticide that is banned globally by the Stockholm Convention on Persistent Organic Pollutants. Under CASRN 8001-35-2, the EPA has categorized toxaphene as a probable human carcinogen (B2) with a cancer slope factor of 1.1 per mg/kg/day, based on long-term mouse and rat studies. There is no oral reference dose.

In addition, a review of CDC's outbreak database did not identify any outbreaks related to Siluriformes or catfish since 2007. A single catfish-related outbreak, with two cases, occurred in 2007, however, the agent or microorganism responsible for the illnesses was not identified.

Addendum References

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