Peer Review Comments and Responses to a DRAFT Risk Assessment for the Public Health Impact of Highly Pathogenic Avian Influenza Virus in Poultry, Shell Eggs, and Egg Products

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

May 2010

Table of contents

1 INTRODUCTION

This document provides responses to comments provided by five external peer reviewers to a version of the risk assessment entitled "DRAFT Risk Assessment for the Public Health Impact of Highly Pathogenic Avian Influenza Virus in Poultry, Shell Eggs, and Egg Products" dated March 14th, 2007.

We provide the reviewers responses verbatim[1]. After every paragraph of their general comments and specific comments, we provide a response. Responses are in arial font and indented. Sections referred to outside of this document (*e.g.,* Appendix A) can be found in the main report, entitled, "DRAFT Interagency Risk Assessment for the Public Health Impact of Highly Pathogenic Avian Influenza Virus in Poultry, Shell Eggs, and Egg Products April 2008." All comments and responses are numbered (from 1 to 230) but are not otherwise labeled.

2 REVIEWERS

An independent, external peer review of this risk assessment was conducted under contract with Research Triangle Institute (RTI) in May 2007. The contract was conducted in a manner consistent with current OMB Peer review Guidelines (http://www.whitehouse.gov/omb/memoranda/fy2005/m05-03.pdf). Under these OMB guidelines, Agency information submitted for formal peer review is confidential and not to be distributed. Five scientific/technical experts (*i.e.*, primary disciplines/types of expertise needed for review are modeler/engineer and microbiologist/virologist) were needed to provide an independent review of this risk assessment. RTI identified and chose potential reviewers. The names of the reviewers were withheld until all five reviews were submitted to FSIS.

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

Amirhossein Mokhtari

[1] Reviewers 3 and 4 provided a portion of their comments within a table. Such formatting was removed and the text placed in paragraph format to be consistent with the other three reviewers.

Dr. Mokhtari, who is currently an Environmental Risk Assessor at RTI International (RTI), has extensive experience in environmental and microbial food safety exposure and risk assessment, quantification of variability and uncertainty, and sensitivity analysis of probabilistic and stochastic models. Dr. Mokhtari has served on the review panel and worked on many research projects sponsored particularly by the U.S. Department of Agriculture (USDA), the U.S. Food and Drug Administration (FDA), and the U.S. Environmental Protection Agency (EPA). Dr. Mokhtari currently provides risk assessment support to various clients on a diverse array of projects, including, but not limited to, developing a methodological framework for the fate and transport of pathogens in the environment due to application of biosolids for agricultural purposes; modeling consumer-phase risk assessment for microbial pathogens with considerable impact on the burden of foodborne diseases, such as *Salmonella* and *Listeria monocytogenes*; quantifying transmission dynamics of infectious diseases in the population; and evaluating the role of food handlers in the spread of microbial diseases.

Dr. Mokhtari holds a Ph.D. in Environmental Engineering from North Carolina State University, and a M.S. in Hydraulic Structures and B.S. in Civil Engineering from the University of Tehran.

Greg Paoli

Mr. Paoli leads a consulting firm (Decisionalysis Risk Consultants) specializing in risk assessment and risk management in the field of public health and safety. He has experience in diverse risk domains including microbiological and toxicological hazards, climate change impact assessment, air and water quality, medical and engineering devices as well as risk-based priority-setting across multiple hazards.

Mr. Paoli has served on many committees/panels as an expert including the Expert Committees of the National Roundtable on the Environment and the Economy and is a member of Health Canada's Expert Advisory Committee on Antimicrobial Resistance Risk Assessment. In the United States, Mr. Paoli has served on an Institute of Medicine Committee tasked to Review the USDA E. coli 0157:H7 Farm-to-Table Process Risk Assessment. He was recently appointed to a NRC Committee entitled, *Improving Risk Analysis Approaches Used by the US Environmental Protection Agency*. In addition, Mr. Paoli served for several years on an Expert Panel to develop a Risk Ranking Framework for the US Food and Drug Administration and was on the Peer Review Panel for the Harvard BSE Risk Assessment.

Mr. Paoli earned a Master of Applied Science degree in Systems Design Engineering and a Bachelor's Degree in Electrical and Computer Engineering from the University of Waterloo.

A. Mahdi Saeed

Dr. Saeed has conducted research in infectious disease and epidemiology in the United States for the past twenty years. His major area of research focus has been *Salmonella* Enteritidis infection in humans and the role of poultry and eggs and their impact on food safety. This is a disease of major importance to both human health and the nation's broiler and layer industries. Dr. Saeed has investigated both the pathogenesis and epidemiology of the disease and is now recognized as one of the nation's authorities in the area. He has been instrumental in formulating national strategies for control of *Salmonella* Enteritidis infections, serving both on a technical review committee which modified the national *Salmonella* control regulations as published in the Federal Register and a USDA committee that revised the recommended procedures for *Salmonella* Enteritidis isolation and characterization.

Because of his expertise in *Salmonella* research, the USDA invited Dr. Saeed to participate in the National Spent Hen Survey in which over 50,000 birds were analyzed for *Salmonella* infection during the years of 1991 and 1995. Dr. Saeed received the United States Department of Agriculture Certificate of Appreciation in 1995 for his dedication in serving the goals of animal health and agriculture. He has also worked with the USDA to develop egg testing programs for *Salmonella* Enteritidis and received a USDA special grant to conduct a major epidemiologic and microbiologic study on the prevalence of *Salmonella* Enteritidis in nest run eggs in the Midwestern States' poultry farms. In related research, Dr. Saeed has studied the mechanism of transovarian transmission that leads to the production of *Salmonella* contaminated eggs and has addressed the disease at the food safety level by investigating the effect of refrigeration and storage abuse on the growth of S*almonella* Enteritidis in eggs. Dr. Saeed's *Salmonella* research findings have been reported in national and international symposia, research conferences, and scientific publications.

Donald W. Schaffner

Dr. Schaffner is Extension Specialist in Food Science and Professor at Rutgers, The State University of New Jersey. His research interests include quantitative microbial risk assessment and predictive food microbiology. Dr. Schaffner has authored more than 100 peer-reviewed publications, book chapters and abstracts. He has been the recipient of almost $4 million in grants and contracts, most of which has been in the form of competitive national grants.

Dr. Schaffner has educated thousands of food industry professionals through numerous short courses and workshops in the United States and more than a dozen countries around the world. Dr. Schaffner has served on expert committees for U.S. National Academy of Sciences, the World Health Organization and Food and Agriculture Organization of the United Nations, and has chaired two expert workshops on microbial risk for WHO/FAO. He was most recently a member of Institute of Food Technologists Expert Panel that developed a quantitative risk

ranking framework for the Food and Drug Administration. Dr. Schaffner is currently serving a 5 year term as Editor for the journal *Applied and Environmental Microbiology*. In April 2007, he was also appointed to serve a second term on the National Advisory Committee on Microbial Criteria for Foods (NACMCF). Dr. Schaffner is active in several scientific associations including the International Association for Food Protection, the Institute of Food Technologists, the Society for Risk Analysis, and the American Society for Microbiology.

He holds a B.S. in Food Science from Cornell University and a M.S. and Ph.D. in Food Science and Technology from the University of Georgia.

Ewen Todd

Dr. Todd served as director of the National Food Safety and Toxicology Center (NFSTC) from March 2001 through February 2006. He is an internationally-known expert on foodborne disease and risk assessment. Through his work as a research scientist, he has been involved with the reporting and surveillance of foodborne disease, developed methods to detect *E. coli* O157:H7, shiga toxin-producing *E. coli* and *Salmonella* in food, estimated the number and cost of cases of foodborne disease in Canada and the United States, determined the impact of seafood toxins, and developed quantitative risk assessments for pathogens in foods. Dr. Todd has encouraged foodborne disease prevention and control strategies by promoting the Hazard Analysis Critical Control Points (HACCP) system and worked with Agri-Food Canada to develop model HACCP plans for 30 products. Dr. Todd received his Ph.D. from the Medical Faculty, University of Glasgow, Scotland, in 1968. He immigrated to Canada and joined the Health Protection Branch, Health Canada. He became Head, Contaminated Foods Section. He reached the highest possible level for research scientists in the government (SE-RES-05), based on the excellence of his research and its relevance to the Branch's programs, and received the Excellence in Science Award for 1998. His scientific accomplishments include numerous research papers, reviews, book chapters, booklets, departmental publications, conference proceedings, editorial articles, reports and abstracts. He is an active member of the International Association for Food Protection and has presented at almost all annual meetings since 1974, being a member of the Committee on Communicable Diseases Affecting Man and is its current chairperson, and has served on the Program Review Committee, Journal of Food Protection (JFP) Management Committee, a member of the PDF on Risk Analysis, and is a manuscript reviewer for JFP.

3 EVALUATION CRITERIA

Reviewers were asked to respond to the following set of evaluation criteria to facilitate the organization and presentation of their comments. These "evaluation criteria"

constitute the FSIS "charge to peer reviewers" (as defined in OMB's Peer Review Guideline, December 2004).

a. Is the overall approach for modeling the risk of HPAI from consumption of HPAI-contaminated poultry, shell eggs, and egg products, as described in the report, fundamentally sound? Specifically, is the use of a combination of scenarios, given the availability of data, as opposed to a probabilistic approach, appropriate? Does the combinatorial approach adequately answer the risk management questions and would these models be useful in guiding and prioritizing emergency and preventive measures, and guiding risk communication messages should HPAI be detected in the U.S.? If not, what problems exist and how should they be addressed?

b. Review the available data and derived variables in conjunction with the underlying assumptions used in this risk assessment.

    1) Have all key studies and data been identified? If not, the reviewer must provide additional data sources and citations (where appropriate).
    2) Have the data been correctly interpreted, analyzed, and used in the risk assessment? If not, the reviewer must provide alternate interpretations, analysis, or suggested utilization of the data.
    3) Please address the validity and appropriateness of all input data in the model.

c. Review the complexity of the model. Is the model too complex or not complex enough to adequately address the risk management questions? Is the model over or under parameterized? State whether the model adequately characterizes the uncertainty present and whether variability has been addressed sufficiently. In areas where the reviewer identifies limitations, weakness, or inadequacies, the review must provide alternate data, data analysis, and/or modeling approaches.

d. Evaluate the risk assessment model source code and mathematics.
    1) Are the modeling techniques (model mathematics and equations) appropriate? If not, the reviewer must provide alternate modeling techniques.
    2) Are the methodologies used in the risk assessment for estimating parameters from the data appropriate (*i.e.*, follow scientifically accepted methodologies)? If not, the reviewer must provide an alternate approach.
    3) The reviewer should examine and verify that the data analysis and source code are accurate.

e. Evaluate whether adequate sensitivity analysis has been provided. Have the most important variables in the model been identified? Has an important variable been left out? Has the impact of including or excluding scientific studies or other data been adequately explored? If so, the reviewer must provide an alternate approach

or application for sensitivity analysis and/or identify those parameters that should have been included.

f. Comment on the adequacy of the risk assessment model documentation. Is the report clearly written? Is it complete? Does it follow a logical structure and layout? Is it useful? If not, the reviewer must provide an alternate outline and/or approach for adequately and clearly documenting this risk assessment.

g. Evaluate the approach taken to estimate illnesses due to consumption of HPAI. Does the data derived from the animal model provide a sufficient surrogate upon which to estimate human illnesses? Are there additional methods to better utilize these or other data? If so, what additional approach should be taken?

4 REVIEWER NUMBER 1

Comment 1

General Comments
Scope of the model

The model predicts the number of illnesses that result from the infection of a single flock with HPAI. This fact, and its implications, should be repeated throughout the text whenever a risk estimate is provided.

Response 1

> The risk assessment output also includes the number of human exposures from a chicken, turkey, or a hen flock and the probability that an infected chicken or turkey flock will be sent to slaughter. To address the reviewer's comment, this has been made more explicit in the document. For example: "Separate models to predict human exposure to HPAI from the index flock were developed for poultry meat and eggs. The models estimate human exposure to HPAI from consuming poultry, shell eggs, and egg products given the contamination of a single flock with HPAI."

Comment 2

There is no discussion of how a flock may become infected with HPAI. While this is understandable (as a matter of scope) and not necessary for this particular model's development, it also has led to the exclusion from the model of the possibility of multiple flocks being simultaneously exposed and infected with HPAI and entering the food chain. Poultry farms often contain multiple houses that are in close proximity – while it is stated that transmission between flocks on the same site is not considered, it is plausible that that the same factors that may lead to multiple birds initiating infection in a single house (included in the model) may lead to multiple houses being infected. A specific example presented by the authors that might lead to the infection of multiple birds is infected feed – which is used as a rationale for the scenario of multiple initial infections in a single flock. This could plausibly lead to multiple flocks being infected. It is predicted that one infected flock leads to 796 cases for chicken flocks, 1,214 for turkey flocks. The likelihood that multiple flocks may be exposed is excluded as results from the APHIS model are not available, however the impact should at least be discussed if not explored.

Response 2

> As the commenter acknowledges, it is necessary to limit the scope of the risk assessment to efficiently answer the risk management questions.

Given the proposed work by the USDA's Animal and Plant Health Inspection Service (APHIS) to develop a risk model to explore the probability of multiple flock infections, such work was not pursued. The commenter suggests that despite the fact that such a limitation is reasonable, the report should discuss and explore issues pertaining to multiple flock infection. Though this is certainly an area of interest for regulatory authorities and other stakeholders, it is important to focus the report specifically on those elements that pertain to the risk model. We have therefore chosen not to include additional language and rely upon future risk models that directly address these issues to properly inform the discussion.

Comment 3

Model Concept

The model described in the report is presented as a tool for decision makers to use, developed using a combinatorial approach. The fundamental concept being that the model is intended to be used to explore combinations of scenarios to explore uncertainty. It is clearly stated that the model is presented with a baseline scenario where mean (or most likely) values have been used for the majority of variables. It is unclear how the tool should be used to explore the combinations.

Given the model is described as a tool, and is not intended to produce a particular set of risk estimates, guidance should be provided as to the use of the model in the exploration of combinations and interpreting results. For example, what options are available? While Appendix 1 seems to present model options, the narrative accompanying Appendix 1 is not sufficient to understand what is presented and how to use it. Discussion of what options are built in (through model options like those presented in Appendix 1) and what variables can and should be explored by the user should be presented to ensure full exploitation of the combinatorial approach.

Response 3

The reviewer is correct that the model has been developed as a tool for risk managers to explore what are the risk factors. The model, as the reviewer mentions, does not estimate the most probable scenario. The reviewer is correct that the documentation in this draft version of the report is limited regarding the instructions how to use the model. We have added a user's manual that allows users to navigate the model and explore different scenarios (Appendix A).

Comment 4

Presentation of Results and Conclusions

Results are presented, in some cases with the mean number of illnesses for each time of possible infection of the flock for chicken and turkey. In others, only the mean over all infections times is presented. This presentation of results in some cases is leading to the loss of complete information for decision making and priority setting, and messages which are open to misinterpretation. Here are three specific examples:

The main results that are presented for the baseline model for chicken and turkey are that in the mean case there are 796 cases from an infected chicken flock, 1,214 from an infected turkey flock. The document then states this can be <1 or >6000 cases. The statement that "this can be <1 or >6000 cases" implies that this range is due to the combination of some underlying uncertainties in the model but that they are unlikely outputs. This is an ambiguous presentation of results. What is not stated is that the likelihood of <1 case is equal to that of >6,000 given the structure of the model and the assumption that the time of infection of the flock is equally likely at all points in the rearing period. While the mean result summarizes the expected number of cases, the fact that the model predicts that 1 case is as likely as >6000 cases is key information and should be explicitly presented and discussed.

Response 4

> The reviewer is correct that the likelihood of each scenario is equal at each possible time point in which a chicken or turkey flock could be infected and that the draft report was ambiguous in it presentation of this information. The following text has been added to clarify this issue: "It is important to note that each time interval is just as likely as the next and therefore the number of illnesses that can be expected from an HPAI-positive flock sent to slaughter is dependent on when the flock was infected prior to slaughter."

Comment 5

The time at which a flock is infected strongly drives the estimated number of cases. For example if a chicken flock is exposed 13 hours prior to slaughter, the model predicts 1 illness. Whereas if the flock is exposed 67 hours prior to slaughter the model predicts 3,426 illnesses. However in some cases the model results are presented as the average result over all time periods. A specific example is presented in the scenario analysis looking at the impact of cross-contamination. The scenario examined the impact of increasing the amount of purge fluid ingested via cross contamination, varying the amount from 0.001 ml to 1 ml. The conclusion presented is that if an individual consumes 1 ml compared to 0.001ml that there is an increase of 4 cases. This leads to the statement that "cross-contamination of HPAI is not a significant source of human illness". This conclusion is misleading. The time at which the flock is infected

influences the number of cases resulting from cross-contamination. Using the spreadsheet model the number of cases from cross-contamination were estimated for different amounts of purge fluid ingested and time of infection of the flock. The results are shown in the following table:

Amount of purge fluid ingested	**Number of Cases from Cross-Contamination (given time of infection prior to slaughter in hours, for chicken)**		
	61 hours	**67 hours**	**73 hours**
0.001	<1	2	4
0.01	5	12	30
0.1	20	50	113
1	44	102	224

It can be seen that if a flock is infected 61, 67 or 73 hours prior to slaughter the amount of purge fluid ingested has what could be considered a large impact upon the number of cases. Given all times point of infection are considered equal, the statement that "cross-contamination of HPAI is not a significant source of human illness" may not be considered valid if results for each time of infection were explored.

Response 5

The reviewer correctly notes that for the poultry model the time at which a flock is randomly exposed to HPAI will have an important impact of the number of illnesses predicted by the model. Given this, for each six hour time interval in which a flock could be exposed, the model predicts an associated number of illnesses from both direct consumption of HPAI contaminated chicken or turkey and from indirect consumption, cross-contamination from chicken or turkey. Using the worst case scenario for cross-contamination the follow illnesses are predicted for both direct and indirect HPAI ingestion:

Time flock infected before slaughter	Number of Cases from Chicken		
	Cross-contamination	Direct Consumption	%
67 hours	1.330105	1.363728	2.5
73 hours	3.170613	3.250822	2.5
79 hours	4.469859	4.582894	2.5

The model predicts that given the worst case scenario of a flock being infected 79 hours before slaughter and not being detected (assuming other baseline assumptions) could result in cross-contamination contributing to an additional 2.5% of illnesses. This suggests that approximately 97% of illnesses are from direct consumption.

The statement in the report "cross-contamination of HPAI is not a significant source of human illness" was meant to demonstrate that in comparison to direct consumption, it is a trivial source of the total number of illnesses. To clarify, the following text has been added: "At the fraction HPAI is assumed to be cross-contaminated (~0.53%) from poultry and subsequently ingested (see Section 4.4.5.4 "Poultry Preparation Module,

Cross-contamination"), cross-contamination of HPAI is not a significant source of human illnesses in comparison to the number of predicted illnesses from direct-consumption."

Comment 6

When examining the number of birds initially infected it is stated that the model is "fairly insensitive to changes in the initial number of birds infected" yet varying it from 1 to 10 birds initially infected leads to an increase of 1.2-fold, increasing from 1 to 100 gives an increase of 1.6-fold and from 1 to 1,000 is an increase of 2.4 fold for the average number of cases. This is another instance where examining the mean output is misleading. Examining Table 27 (page 81) it is clear that at any time point of infection increasing the number of initially infected birds has a much greater impact than is implied by the mean effect, for example, from Table 27 increasing from 1 initial infected has the following impacts: at infection 1 hour prior to slaughter the number of cases increases from 0 to 98, at 7 hours increases from 0 to 437 illnesses etc. Going from 1 to 10 infected in most cases has an impact of a 10 fold increase. The result that the mean impact is 2.4 is reliant upon the assumption that flocks will be identified sooner and not sent to slaughter but discussion of this result in isolation suppresses the importance of the initial number infected in cases where the flock does go to slaughter. The conclusions drawn should be reconsidered as it implies that further consideration of the possibility of multiple introductions as the source of infection in a flock is not an important issue.

Response 6

The reviewer is correct. Focus on average illnesses during these sets of scenario analyses does not tell the entire story. Within a particular 6-hour time block varying the number of chickens or turkey initially infected results in an approximate 10-fold increase in the number of predicted human illnesses. The text has been modified to reflect the impact of these scenarios on the model output: "However, if a flock is still sent to slaughter (daily mortality < 2.0%), more birds will be infected given the fact that more birds were initially infected. Therefore there is greater exposure due to more poultry carcass being infected and more predicted human illnesses from poultry consumption. Varying the initial number of infected birds 10-fold result in an approximate 10-fold increase in predicted human illnesses (Table 29)."

Comment 7

A similar statement is made regarding eggs, however detailed results are not presented, only the statement that "the impact is always less than 2-fold".

Response 7

The reviewer was provided the egg model spreadsheets (AI Model 070227 Eggs a.xls) and could have generated the results. Using this spreadsheet, the following table was produced:

Initial # of hens infected	Predicted illnesses
1	90
10	122
100	100
1,000	61
10,000	0

The egg model does not generate multiple scenarios based on the time the flock is infected. Therefore, the results represent the baseline scenario and not an average.

Comment 8

Is the overall approach for modeling the risk of HPAI from consumption of HPAI-contaminated poultry, shell eggs, and egg products, as described in the report, fundamentally sound? Specifically, is the use of a combination of scenarios, given the availability of data, as opposed to a probabilistic approach, appropriate? Does the combinatorial approach adequately answer the risk management questions and would these models be useful in guiding and prioritizing emergency and preventive measures, and guiding risk communication messages should HPAI be detected in the U.S.? If not, what problems exist and how should they be addressed?

The overall approach is that of a farm-to-fork risk assessment approach considering all stages from initial infection of the livestock species (broiler, turkey and layer hens) through to preparation, consumption and illness in consumers of the resulting meat and eggs. This approach is commonplace for microbial assessments of this type and is generally appropriate.

The underlying concept with the combinatorial approach as described by the authors is that uncertainty is handled through a series of What-If scenarios which are handled through re-run of the models with different sets of parameters entered in the model. The model is presented as a Baseline model using a mix of mean value and probabilistic treatments, for example the number of birds in a chicken/turkey/layer flock is set to the mean value of available data, where as the time of infection is simulated as a random event.

A limitation of the combinatorial approach is in ensuring the combinations of parameters are fully explored. While use of the combinatorial approach is an acknowledgement by the authors of the high degree of uncertainty associated with many model parameters, it also lends itself to an approach which can result in considerable underestimation (or the lack of exploration) of the overall uncertainty. This is because the approach relies solely

on the user to explore the full extent of uncertainty (and variability in some cases) and all combinations thereof.

Response 8

> The reviewer suggests that the combinatorial approach could result in an "underestimation (or the lack of exploration) of the overall uncertainty … because the approach relies solely on the user to explore the full extent of uncertainty". To explore much of the uncertainty in the model, the authors have used the risk model to run a sensitivity analysis for all parameters. These results are reported in the Risk Characterization of the main report, Section 6.3.1.

Comment 9

For some variables there are data available to fully characterize the variation, for example flock size and the number weeks in house (and others) according to Table 2. It is likely that the combination of larger flock size and longer time in house will result in more cases of illness from that flock and that this is something a user may want to explore (for example in answer to the question – how many cases might be expected if the flock that is infected is 5 times bigger than the baseline? Use of the data to fully characterize these parameters (and others) could allow the reservation of the combinatorial approach for variables which are truly unknown or have high uncertainty – enabling more efficient use of the model in exploring the full extent of uncertain components of the model.

Response 9

> A baseline model informed by the expected values was developed. This allows model users to change those input and then compare the results back to the baseline. There is little attempt by the authors to systematically qualify which parameters are likely variable or uncertain. The data sources and assumptions are described in the report and it is up to the users to choose which model inputs to modify to suit their specific needs.

Comment 10

It is important that the authors, while defending and justifying the combinatorial approach, do not oversell the approach. At one point, it is said to 'fully characterize the uncertainty.' This is far from the case. Such 'marketing' statements undermine the rationale for what may be a reasonable decision to choose a combinatorial approach (as long as the analysts 'finish the job' of actually characterizing uncertainty as they have promised in the text).

Response 10

The following statement “fully characterize the uncertainty” has been changed to “characterize the uncertainty”. In addition, a structured sensitivity analysis has been completed allowing the authors to rank risk factors (see Section 6.3.1).

Comment 11

The arguments against the Monte Carlo approach (essentially requiring 10 trillion iterations) are technically inadequate as a form of justification for the combinatorial approach. It is not necessary to simulate a 1 in 10 trillion event in order to provide a reasonable characterization of the output distribution. They are further inadequate in that the need to characterize the risk at such extremes (i.e., what Monte Carlo could not easily do) is not provided in the risk assessment.

Response 11

It is not the purpose of the model “to provide a reasonable characterization of the output distribution.” Rather, the purpose is to show the range of outputs that is possible and what combinations of inputs lead to the highest risk outputs.

Comment 12

The risk assessment report should provide an adequate exploration of the full range of uncertainties, even if only as a bounding approach. This is necessary to meet the obligation to describe the extent of uncertainty in the numbers presented as well as to demonstrate (as a form of guidance) the range of uncertainty to be expected when the user explores uncertainty on their own. This process will necessarily expose the

Response 12

The reviewer is correct. As mentioned above, a sensitivity analysis of all parameters was completed using minimum and maximum values. See Section 6.3.1 in the main report.

The reviewer was contacted to determine the meaning of the following statement, “This process will necessarily expose the”; however, a completed response was not received.

Comment 13

An overriding concern with the approach is the apparent arbitrariness of the approach in terms of which parts of the model are dealt with by actually describing and employing variability in calculation or simulation (e.g., in infection time, thoroughness of cooking), which readily characterized variabilities are suppressed (such as flock size), and which uncertainties are suppressed (and only available through the combinatorial approach). If the choices are not arbitrary, then the strategy should be explained.

Response 13

The reviewer is correct that there was not a hierarchical overreaching structure used to determine which variables received additional scenario analysis. All poultry model and egg model variables were analyzed for impact on model outputs. However, no system was used to rank which model inputs had the greatest impact. As indicated above, a sensitivity analysis has now been conducted using the combinatorial approach. See Section 6.3.1

Comment 14

The authors should avoid using the term "mean" for results when the averaging is occurring over only one variable (such as infection time). The baseline result (even if one component of the model is simulated) is simply a calculation result with largely unknown statistical properties. It is well known (and well known by these authors) that propagating a loose collection of central estimates (e.g., means, most likely values) through a complex, probabilistic and non-linear does not result in a value that has predictable statistical properties (and therefore shouldn't be given the label 'mean').

Response 14

We concur with the reviewer. We have replaced "mean" with the term "central value" which has no mathematical meaning but conveys the sense that we are attempting to estimate an output somewhere in the middle of possible outputs.

Comment 15

Review the available data and derived variables in conjunction with the underlying assumptions used in this risk assessment.

1) **Have all key studies and data been identified? If not, the reviewer shall provide additional data sources and citations (where appropriate).**

2) **Have the data been correctly interpreted, analyzed, and used in the risk assessment? If not, the reviewer shall provide alternate interpretations, analysis, or suggested utilization of the data.**

3) **Please address the validity and appropriateness of all input data in the model.**

The review has not included an audit of the cited literature to determine whether assumptions that are ascribed to other sources or documents are properly represented. Detailed audit of the scientific evidence and available literature is time-consuming and requires domain-specific expertise. As a result, in order to focus the effort of this peer review on technical implementation, detailed consideration of supporting scientific evidence was not considered.

Given this caveat, there remains some confusion about the value assigned to some model variables:

- The model assumes live weight of turkey of 40lbs yet it states that the National Turkey Federation sourcebook state an overall average of 28.1lbs. This is less than the assumed weight. Why was 40lbs chosen?

Response 15

The footnote incorrectly depicts how the model uses bird weight and has been removed. The following text has been added to the risk assessment report: ""Weeks in House" refers to the number of weeks a flock is reared for production (the grow-out period). The duration of the grow-out period is dependent on the type of subspecies of poultry (Table 3). The longer birds are reared, in general, the larger they will grow. Therefore, as different grow-out periods (weeks in house) are chosen, the model automatically simulates an individual bird weight commensurate with the grow-out period."

Comment 16

Review the complexity of the model. Is the model too complex or not complex enough to adequately address the risk management questions? Is the model over or under parameterized? State whether the model adequately characterizes the uncertainty present and whether variability has been addressed sufficiently. In areas where the reviewer identifies limitations, weakness, or inadequacies, the review shall provide alternate data, data analysis, and/or modeling approaches.

The model structure considers the main stages of production of chicken/turkey and eggs and provides a sufficient level of mathematical description of these processes given the overall uncertainties that exist when considering HPAI as a zoonotic pathogen. The

model propagates mean values through the model to represent variable components, with the exception of time of introduction of infection. This approach reduces the complexity of the model in terms of computational complexity and the complexity of the data required to populate the model. However there is concern that uncertainty analysis is left to the user to explore. To truly explore the uncertainty many combinations should be explored and this is not discussed in the accompanying documentation.

Response 16

See response 8. The authors of this report do acknowledge that the uncertainty analysis as presented in the draft report provided to reviewers does not systematically nor completely explore the uncertainty. A better job can be done using the current version of the model. Therefore, we have conducted a more thorough sensitivity analysis to explore uncertainty within the model and reported these results within the report. See Section 6.3.

Comment 17

It also needs to be recognised that analysis of the variation will also form part of the analysis of model outputs and should be recognised as a process the User will manually need to perform. It is reasonable to expect that the worse case scenario(s) will be of interest in terms of the variability and not only uncertainty. For example the combination of one of the larger flock sizes present in the industry, infection 73 hours prior to slaughter, and combinations of the uncertainty for parameters such as dose-response, amount of purge fluid consumed etc. The exploration of scenarios (or combinations) and interpretation of the results is a complex and time consuming process and support is required in how to approach such a process ensuring that full analysis is performed for decision making and not simply obvious combinations, or a limited number because of time constraints. Guidance on what might be worse case assumptions, and the likelihood of these worse case assumptions (for example infection 73 hours prior to slaughter compared to 1 hour offers a worse case, but is just as likely, where as a flock size approaching the maximum size for industry will also present a worse case but will have a known and much lower likelihood), which parameters are truly unknown, which parameters are uncertain but have plausible limits etc. This information would aid in the use of the tool to explore uncertainty and use the information in a decision support process.

Response 17

The worst case scenario is not necessarily useful to decision makers. The report currently informs decision makers that the poultry model predicts approximately 14 human illnesses if a turkey flock is infected 73 hours prior to infection. Whether this number is greater given the assumptions of a worst case scenario is not of importance. The model indicates where

the risk currently is—that is from flocks infected close to the time they are to reach market weight. The model can then be used to show what would be the relative risk reduction if testing of flocks prior to slaughter was implemented. The usefulness of the model is to identify those risk factors that result in large numbers of exposures and illnesses and then determine the effectiveness of mitigating those effects.

To address the reviewer's comments, again, a sensitivity analysis was completed using the minimum and maximum values for all parameters. This process, besides ranking and identifying the most influential model parameters, also has produced a worst case scenario.

Comment 18

There is some concern regarding the manner that mean values are propagated through the model in place of probabilistic treatments of variation. From interpretation of the review materials it appears that the mean estimates and the select variables described randomly are combined to give a mean estimate of the dose ingested with some variation provided by, for example day of infection. This is then used in the dose response model to estimate the risk. This would result in the mean risk, and hence number of illnesses if the overall risk assessment model were linear in nature. However the dose-response model is not a linear model. In some circumstances the assumption of a linear model may be appropriate, specifically when it is reasonably certain the combination of the level of exposure and the value of the dose response parameter results in exposures in the linear portion of the exponential dose response model, for example the exponential model is linear in the low dose region. If the model is not linear then propagation of the mean dose through the dose response model is not equivalent to the propagation of individual, variable doses and estimating the resulting mean risk. This is illustrated in the table below. For the example doses given it can be seen that the mean dose is 23,202, this results in a risk estimate of 0.9. However, using individual doses and calculating the mean gives a risk estimate of 0.42. Given that the dose response parameter r is highly uncertain, options are provided in the spreadsheet model for the value of r users should be encouraged to explore the impact of r on model results. However, when r values, and other model variables can be changed by the user (in line with the combinatorial approach adopted) it cannot be assured that the levels of exposure (dose) will be limited to the linear portions of the dose-response model. Therefore where the variability in a model component was suppressed and mean estimates were used for components that may affect the variation in doses the variation in the components should be described probabilistically.

	Risk Given r		
Dose	**R = 0.0001**	**R = 0.00001**	**R = 0.000001**
10	1.0E-03	1.0E-04	1.0E-05
1,000	9.5E-02	1.0E-02	1.0E-03
5,000	0.39	0.05	0.00
10,000	0.63	0.10	0.01
100,000	1.00	0.63	0.10
Average of risk when calculated by individual dose	0.42	0.16	0.02
Average dose = 23,202	0.90	0.21	0.02

Response 18

If the exponential dose-response relationship was developed using average dose, then that is the argument to enter into its calculation. It would be incorrect to use the true dose in this equation. The exponential dose-response equation is derived by assuming dose is Poisson distributed and the probability of each organism actually ingested causing illness/infection is binomial.

It is not clear what this comment means. Is 23,202 thought to be the average dose delivered? If so, that is not the case in the model.

Comment 19

One component where an increase in complexity may be beneficial to the model is in the cooking model. Cooking occasions are grouped in to one of four temperature treatments: 135, 145, 155 and 165 F. The move from the bin 145F to the bin 155F has a very large impact upon the log reductions obtained through cooking, in some cases going from <1 $\log_{10}$ reduction at 145F to >10 $\log_{10}$ reductions at 155F depending upon which cooking model option is selected. This results in an almost "All or nothing" result from cooking, the product either receives practically no inactivation through cooking (135 and 145F bins) or the virus is likely to be eliminated as a result cooking (155 and 165F bins). Some consideration might be given to increasing the granularity of cooking temperatures modeled in the range from 145 to 155F will result in better estimates of the impact of cooking.

Response 19

The reviewer is correct that less aggregated data would allow for a more refined analysis leading to a more refined risk communication message. However, the aggregated data allows the model to estimate the effect of cooking as well as possible mitigation strategies. Additional refinement of the data is not likely to change the risk communication message supported by the risk assessment that cooking to the FSIS recommended temperature of 165 ^{o}F will protect consumers from exposure to HPAI.

Comment 20

Evaluate the risk assessment model source code and mathematics. Are the modeling techniques (model mathematics and equations) appropriate? If not, the reviewer shall provide alternate modeling techniques. Are the methodologies used in the risk assessment for estimating parameters from the data appropriate (i.e., follow scientifically accepted methodologies)? If not, the reviewer shall provide an alternate approach. The reviewer should examine and verify that the data analysis and source code are accurate.

It is not possible to fully evaluate the model source code and mathematics. The model mathematics and equations are only described at a superficial level of detail in the report, since essentially no equations were provided. Based upon the qualitative description of the modelling approach the techniques appear to be appropriate however this cannot be confirmed without explicit presentation of the modelling techniques and rationale for approaches used.

Response 20

The reviewer is correct that additional documentation was needed within the report. As a result, both a user's manual and a mathematical model description have been developed (see Appendix A and C).

Comment 21

The model equations are not provided in the documentation and therefore the source code cannot be checked for accuracy in terms of the implementation of intended equations. Through examination of the spreadsheets, the model seems to be implemented as intended but this becomes an educated guess that it is appropriate. A few things were noted while examining the Meat spreadsheet model:

It was noted that it is calculated that there are, on average 244 servings per bird for turkey and 34 servings per bird for chicken (see sheet Slaughtermodel M7). It may be that the cell is mislabelled, however following the calculation it appears that the value is used as a serving size. If this is indeed the serving size then this cell must be calculated incorrectly. There is no mention of how serving size is derived and used in the technical document so it cannot be confirmed. One possible cause is the use of the CSFII data to derive the serving size. The data presented are EDI which presumably is the estimated daily intake. This is not necessarily the same as the average serving size given consumption of a serving chicken/turkey. It should be confirmed that the data used is

serving size given consumption occurs, and that it does not include days when no consumption of chicken/turkey occurs.

Response 21

The reviewer is correct that estimate daily intake (EDI) was not the appropriate metric. This has been change. However, the servings per bird and serving sizes are calculated correctly. The average serving size for turkey is smaller than the average serving size for chicken, although both products have a 99th percentile of over 336 grams.

The following text has been added: "To estimate the average number of servings consumed, the 1994-1996, 1998 USDA Continuing Survey Food Intake by Individuals (CSFII) was used. The grams per serving was derived from consumers only and are an average of a two survey days. The population group is male and female, ages 2 and older. Foods were excluded if they did not contain poultry and/or eggs or if they were ready-to-eat, such as jarred and canned foods, including baby foods (Table 8)."

Table 1. Turkey, chicken, and egg consumption (CFSII 1994-1996, 1998).

	Turkey	Chicken	Egg
mean (g)	60.6	83	19.8
Percentile			
10	15.8	9.4	0.5
20	21.3	26.7	1.2
25	24.7	36.2	1.6
30	28	44.7	2.1
40	32.6	56.7	3.4
50	42.6	72.3	5.3
60	53	85.5	8.4
70	59.6	97.4	14.9
75	67.2	103.1	21.6
80	83.5	119	37
90	113.9	170	73.3
95	169.8	209.8	87.4
97.5	224.1	254.3	101.2
99	336.1	338.8	139.8
99.5	425.6	379.2	168.7
99.9	859.5	582.3	257.5
100	1220	928.8	450.6

Comment 22

It does not appear that the cap in the EID50/gram is implemented as described in the text. See sheet Slaughtermodel I20:I32, the value exceeds 10 log10 EID50 per gram yet the technical reports describes a cap at 7.4 log10 EID50 per gram.

Response 22

The review is correct that the SlaughterModule worksheet does indicate higher levels per gram than the actual experimental level. However, the cap was implemented correctly further downstream within the model. To test this, rows S16-19 in ModelOptionsChicken can be modified with different HPAI levels. Such a change has no effect on the output of the model.

Comment 23

Similarly the data used in the model and method of analysis of the data are not described for all data used in the model. However, the use of the consumption data EDI needs to be checked (see above comment).

Response 23

See Responses 20 and 21.

Comment 24

Evaluate whether adequate sensitivity analysis has been provided. Have the most important variables in the model been identified? Has an important variable been left out? Has the impact of including or excluding scientific studies or other data been adequately explored? If so, the reviewer shall provide an alternate approach or application for sensitivity analysis and/or identify those parameters that should have been included.

Full scenario analysis of the model is not presented. In part this in inline with the concept of a combinatorial approach where a user is encouraged to perform analysis of the model.

Noticeably missing from the scenario analysis is an examination of the impact of the model for the change in the EID_{50} over time. The baseline results will be highly sensitive to the assumption of how the number of EID_{50} per gram changes over time. This is assumed to be a linear model increasing to a maximum of 7.3 $\log_{10}$ EID_{50} per gram. Although it is presented that the model options allow the user to have a 10-fold increase or decrease in the level. Given the almost complete uncertainty associated with this model, an exploration of the impact of different assumptions regarding this model should be presented in the report alongside the exploration of other assumptions. Note that the figure does not show the cap used in the model, the figure allows the level to increase to >10 $\log_{10}$ EID_{50} per gram over time. The spreadsheet model also seems to allow levels greater than the cap suggested in the text, it should be confirmed that this cap is implemented in the model.

Response 24

As the reviewer notes, the model allows the user to alter the maximum allowed level of HPAI by a 10-fold increase or decrease. This has the effect of changing the level at each 6-hour time interval by 10-fold. In the report, the level was decreased by up to 10,000-fold to demonstrate the effect of lower HPAI in poultry meat. Though the reviewer is correct that there is not a direct analysis to address how the levels change over time, altering the level by several orders of magnitude demonstrates that the model is sensitive to levels. See Section 4.4.4.3 for a revised write up on estimating HPAI levels prior to peak infection. See Section 6.3.3.3 for sensitivity analysis of levels.

See Response 22 regarding cap of levels.

Comment 25

The dose response model is highly uncertain. Figure 6 presents alternate assumptions for the value of r. These should be explored in the sensitivity analysis, and users encouraged to explore the impact of this as one of the uncertainties of the model.

Response 25

The following table has been added to the risk assessment report to help the user explore the different values of *r* and their impact on the model results.

Study	Strain	Model	ID_{50} (EID_{50})	*r* = ln(2)/MID50	Average human illnesses
Beare and Webster, 1991	H6	Human	NA	2.40E-10	0
Beare and Webster, 1991	Avergae of all strains (H1,H3,H6,H4, H9, H10)	Human	NA	1.35E-09	1
Beare and Webster, 1991	H3	Human	NA	4.00E-09	3
Beare and Webster, 1991	H1	Human	NA	5.80E-09	4
Beare and Webster, 1991	H4, H9, H10	Human	NA	1.20E-08	9
Sears et al.,1988	H1N1 and H3N2	Human	3.16E+06[1]	2.19E-07	139
Sears et al.,1988	H1N1 and H3N2	Human	2.51E+06[1]	2.76E-07	169
Clements et al., 1989	H3N2	Human	2.00E+06[1]	3.47E-07	203
Mase et al., 2005b	H5N1(Dk/Yokohama/aq10/2003)	Mouse	1.60E+06	4.33E-07	241
Clements et al., 1986	H3N2	Human	1.58E+06[1]	4.37E-07	243
Clements et al., 1989	H3N2	Human	6.31E+05[1]	1.10E-06	463
Maines et al., 2005	H5N1 (CkNCVD8)	Mouse	6.31E+05	1.10E-06	463
Snyder et al.,1986	H1N1 and H3N2	Human	2.51E+05[1]	2.76E-06	771
Sears et al.,1988	H1N1 and H3N2	Human	2.51E+05[1]	2.76E-06	771
Maines et al., 2005	H5N1 (CkIndon)	Mouse	2.00E+05	3.47E-06	858
Clements et al., 1983	H3N2	Human	2.00E+05[1]	3.47E-06	858
Snyder et al.,1986	H1N1 and H3N2	Human	7.94E+04[1]	8.73E-06	1232
Sears et al.,1988	H1N1 and H3N2	Human	7.94E+04[1]	8.73E-06	1232
Nguyen et al., 2005	H5N2 (Dk/VN/342/01)	Mouse	6.31E+04	1.10E-05	1330
Nguyen et al., 2005	H5N1 (Gs/VN/113/01)	Mouse	2.00E+04	3.47E-05	1812
Maines et al., 2005	H5N1 (CkCNVD31)	Mouse	3.16E+03	2.19E-04	2378
Lu et al., 1999	H5N1 (HK/156)	Mouse	1.58E+03	4.39E-04	2494
Maines et al., 2005	H5N1 (VN1204)	Mouse	2.00E+02	3.47E-03	2620
Maines et al., 2005	H5N1 (CkKorea)	Mouse	2.00E+02	3.47E-03	2620
Lu et al., 1999	H5N1 (HK/483)	Mouse	1.58E+02	4.39E-03	2624
Maines et al., 2005	H5N1 (VN1203)	Mouse	6.31E+01	1.10E-02	2631
Maines et al., 2005	H5N1 (SP83)	Mouse	6.31E+01	1.10E-02	2631
Maines et al., 2005	H5N1 (Thai16)	Mouse	2.00E+01	3.47E-02	2632
Lu et al., 1999	H5N1 (HK/486)	Mouse	1.58E+01	4.39E-02	2632
Lu et al., 1999	H5N1 (HK/485)	Mouse	1.26E+01	5.50E-02	2632
Nguyen et al., 2005	H5N1 (HK/483/97)	Mouse	3.16E+00	2.19E-01	2632

Comment 26

Turkey tables are inconsistent in presentation of results – all chicken results are shown for up to 73 hours infection prior to slaughter – this standardization of presentation for chicken would aid in the comparison of chicken and turkey scenarios.

Response 26

The chicken results were shown to 73 hours because the model predicts that chicken flocks have up to a 73 hour risky time window of being sent to slaughter. Alternatively for turkeys, the model predicts that this window is smaller by 6 hours.

Comment 27

Comment on the adequacy of the risk assessment model documentation. Is the report clearly written? Is it complete? Does it follow a logical structure and layout? Is it useful? If not, the reviewer shall provide an alternate outline and/or approach for adequately and clearly documenting this risk assessment.

The report describing the model presents a top-level description of the model. Most components of the model are described in some form. However, there is very little technical detail presented in the report. For example there is a noticeable absence of any mathematical equations (with the exception of the dose-response model). While it is appreciated that documents can and should be presented with levels of detail as appropriate for the audience, the document does not constitute a technical report with respect to the implementation of the risk assessment model. Reasonable detail is provided regarding the evidence base for the analysis, but the document does not describe the computational aspects of the model. In its present form, the level of detail is insufficient to understand the mechanics of the model without detailed scrutiny of individual cells in the spreadsheet. In the end, readers and reviewers must rely on a general impression of the model, rather than certainty as to how the calculations are done.

In addition, the spreadsheet model is not transparent in presentation. This, combined with the lack of technical detail in the technical report results in the full review process being almost intractable.

The model is designed to be used as a tool to explore combinations of parameter yet there is no discussion or guidance provided in the report as to how to use the model to explore combinations. This makes the combinatorial approach a much higher risk product than it otherwise needs to be.

Response 27

The reviewer is correct. As a result, a mathematical description of the parameters has been added to the text along with a user's manual (See Appendix C and A, respectively).

Comment 28

As a result of the lack of transparency and technical detail it is not possible to fully determine if the results presented in the report are reasonable. For example:

Section 6.1.3 presents the number of illnesses expected given different times of infection of a single poultry flock prior to slaughter. A turkey flock infected 67 hours prior to slaughter is expected to result in 6,478 illnesses. The results for 72 hours are not provided but would be expected to be larger than 6,500 illnesses. To evaluate if these results are reasonable is not possible for the following reasons:

- It is not possible from the report to evaluate the proportion of a flock that would be infected at slaughter if infected 67 or 73 hours prior to slaughter

Response 28

Proportions of flocks are not evaluated by this risk assessment. A flock is defined as the number of birds in a single house. As stated in the report, as poultry slaughter is an all in all out process, the entire house, if infected with HPAI, will either be detected or sent to slaughter. The model predicted that a turkey flock exposed at HPAI 73 hours prior to when the flock is supposed to be sent to slaughter, will not be sent to slaughter. This is why the data were not shown.

Comment 29

The baseline assumptions for the level of inactivation by cooking are not presented in the report, what log reductions are achieved for different cooking temperatures? In the introduction it states that 165F is sufficient to eliminate the virus. In Table 6 it states that 57% of poultry will be cooked to greater than 165F. Any virus in this percentage of poultry is likely to be eliminated. From the spreadsheet model at 155F 10 log reductions are achieved under baseline assumptions but this is not presented the report.

Response 29

The reviewer is correct that the cooking section in the report needs to be further elaborated. However, the baseline assumptions and how they were derived were in the material provided (AI Model 0703005 Meat a, spreadsheets "Cooking" and "CookingFDAAnalysis").

Comment 30

For cross-contamination, 0.0126 of virus in a poultry product is assumed to be present in the purge and therefore may be available for consumption as a result of cross contamination. The baseline assumption of how much of this is consumed is not presented in the report and is not clear in the spreadsheet.

Response 30

How much is consumed following cross-contamination is up to the user of the model. The baseline model does not incorporate cross-contamination. This is because the model does not estimate the fraction of servings from chicken, turkey or shell eggs that will be cross-contaminated. If this component of the model is on, then it is assumed all servings result in cross-contamination. The text has been modified to reflect this.

Comment 31

The number of servings from 1 carcass and therefore 1 flock is not presented in the report. From the spreadsheet this appears to be incorrectly calculated (as discussed earlier) and may be resulting in much larger predicted illnesses than would be expected given the baseline scenario.

Response 31

See Response 21.

Comment 32

Evaluate the approach taken to estimate illnesses due to consumption of HPAI. Does the data derived from the animal model provide a sufficient surrogate upon which to estimate human illnesses? Are there additional methods to better utilize these or other data? If so, what additional approach should be taken?

This reviewer does not have sufficient information from what is presented, nor the expertise to fully scrutinize the judgments that are applied in the animal to human extrapolation.

A concern that arises is the inclusion of a value for r that is deliberately and admittedly 'conservative' (i.e., by not taking account of the species and pathway extrapolations that are likely to bias significantly in the same direction toward a lower value for *r*). This has

the potential to undermine the risk assessment process since there is no guidance as to where a best estimate might be located, and the entire assessment could become labelled 'conservative' when it may (overall) be quite the opposite when other variables (particularly the impact of variability) are considered. A baseline value for *r* that cannot be readily labelled either conservative or anti-conservative should be chosen (even if not appropriately given the label of a best or central estimate of the uncertainty in *r*).

Response 32

In response to the reviewer's comment, a human intranasal inoculation trial has been used to develop a dose-response and compared to the mouse data and model. See Section 5 in main report.

5 REVIEWER NUMBER 2

Review of
"Risk Assessment for Highly Pathogenic Avian Influenza"

a. Is the overall approach for modeling the risk of HPAI from consumption of HPAI-contaminated poultry, shell eggs, and egg products, as described in the report, fundamentally sound? Specifically, is the use of a combination of scenarios, given the availability of data, as opposed to a probabilistic approach, appropriate? Does the combinatorial approach adequately answer the risk management questions and would these models be useful in guiding and prioritizing emergency and preventive measures, and guiding risk communication messages should HPAI be detected in the U.S.? If not, what problems exist and how should they be addressed?

Comment 33

The overall approach used for risk assessment of highly pathogenic avian influenza, as described in the Report, has few shortcomings that undermines the suitability of the algorithm and insights from the analysis for use in risk management or policy decision-making. In this review, it has been attempted to identify and expand upon the critical problems with the approach and suggest alternative methodologies. However, it is recommend that such suggestions be tested and their suitability verified using available data before any substantial conclusions be reached. The shortcomings discussed in this review include the combinatorial analysis, modeling approach used for estimating within-flock prevalence, modeling approach used for the egg preparation model, and methods used for sensitivity analysis. The first shortcoming is discussed in the following, while the rest are discussed in responses to the charge questions *c* and *e*, respectively, and are not repeated here.

Response 33

No response necessary here. Comments are addressed individually below.

Comment 34

The first shortcoming is regarding the methodology used to evaluate uncertainty in the model as *combinatorial analysis*. As explained in the Report on Page 26, the combinatorial modeling approach is different from a probabilistic Monte Carlo analysis. In a Monte Carlo simulation, each model variable is represented by a probability distribution that describes the likelihood of all possible values of a variable from the least

to the most likely. Monte Carlo analysis then draws from these different probability distributions in each model simulation to characterize the variability inherent in the natural system. However, the authors argued that Monte Carlo technique was not applicable to this study as there were not enough data to build corresponding probability distributions for the model inputs. Thus, the combinatorial approach was implemented to fully characterize the effect of *uncertainty*.

The reviewer believes that it is not clear if the authors tried to address variability, uncertainty, or both in their data and model using combinatorial analysis. In fact, the reviewer believes that this approach has a major shortcoming when it is applied to a model that includes both variability and uncertainty. Uncertainty, also known as epistemic or subjective uncertainty, represents the lack of perfect knowledge of an input and can be reduced by further measurements. Variability, however, represents a true heterogeneity in the population, and cannot be reduced by further measurement (Murphy, 1998; Anderson and Hattis, 1999; Cullen and Frey, 1999). It is not always possible to separate uncertainty and variability in inputs. There is often limited information about the form of an input distribution and its underlying uncertainty and variability. Nonetheless, making the simplifying assumption of treating uncertainty or variability as one can substantially affect the outcome of the risk assessment. Thus, when the nature of the probability distribution of an input is not clear, it may be better to imprecisely assign the input as uncertain and/or variable than not to separate them at all (Nauta, 2000).

Response 34

Each iteration of the model simulates variability in time of flock infection, cooking practices, and serving size. In all, 56 different infection times, 5 different cooking practices, and 19 different serving sizes are modeled. Rather than drawing from variability distributions, however, each combination of these inputs informs the model either simultaneously or in sequence. The results for the iteration are weighted by the probability of occurrence of each of the variable inputs just as they would be in a Monte Carlo model. These calculations can be thought of as the inner loop of a 2^{nd} order model. In all each uncertainty simulation is informed by calculations for 5320 variability iterations.

Uncertainty in the model is simulated by changing various combinations of inputs in the SummaryModel sheet. This sheet has 15 user changeable inputs. With two exceptions, described below, these changeable inputs all represent uncertainty in the model. Combinations of these inputs can be modeled singly or in multiples up to 65,000 depending on the number of combinations the user wishes to evaluate. Changing different uncertainty inputs allows one to simulate the outer loop of a 2^{nd} order model. The results from this simulation are identical to a Monte Carlo simulation in which all uncertain inputs are represented by discrete uniform distributions.

The two exceptions in the SummaryModel sheet are not meant to represent either variability or uncertainty. Rather, they are meant to evaluate specific scenarios. The two exceptions are for flock size and type of flock. Because only a single flock will be infected as the index flock it was thought to be more important to be able to evaluate specific combinations of flock size and type rather than being able to integrate across all flock sizes and types to give an overall risk for all flocks.

One of the main reasons for using this combinatorial approach is to allow risk managers to evaluate specific event constellations that could result in the highest level of risk regardless of probability of occurrence. Because data for these inputs is so sparse, probabilities for specific constellations of events cannot be reasonably assigned. Although expert judgment might/could be used to generate probability distributions for these uncertain inputs, such an approach wasn't deemed necessary given the scope and nature of the risk management questions. Should firm policy decisions be contemplated, then further characterization of input uncertainties could be pursued.

Comment 35

Authors discussed that they formed a baseline scenario using the *mean* values for the majority input parameters (Page 27). Thus, it can be inferred that the baseline results represent the mean risk imposed to the population based on exposure to foods contaminated with HPAI. Alternative scenarios analyzed using combinatorial analysis represent *uncertainty* associated with the mean values of model inputs, and hence, can quantify *uncertainty* in average value of the risk. However, risk managers are not typically concerned with average risk to the population. Risk management strategies are typically established based on the most exposed or at risk portion of the population (e.g., upper 5 percentile) rather than the average values. In order to quantify the risk imposed to the most exposed portion of the population, it is required to fully propagate variability inherent in the model parameters, and hence, estimate the possible range of variation in the model outcome, i.e., risk. Thus, performing uncertainty only analysis in which variability in model parameters are neglected or deemed to be negligible compared to the range of uncertainty in the model parameters cannot provide insight regarding highly exposed portion of the population. The authors may argue that they used terms such as variability and uncertainty interchangeably and in actuality they tried to capture the range of risk imposed to the population based on possible variation in the model parameters using combinatorial analysis; however, this is not true.

Response 35

As noted before it is not a mean value of a distribution that is used to simulate variability. Rather, variability is simulated by selecting specific

points along with their likelihood of occurrence from probability distributions. The model does, however, report mean risk as the output.

Comment 36

The reviewer believes that changes in some model parameters represented uncertainty in mean values, while for other parameters those changes represented variability in their possible values. For example, the effective contact rate is defined on Page 37 as the number of contacts that produce a new infection per unit time with a range between 1 and 64 which clearly represents variability in this model parameter. In contrast, the true portion of birds that die after 36hrs following exposure to HPAI is a source of uncertainty in the model with a mean value of 0.4 and uncertainty range between 0.2 and 0.6 associated with this mean value (Page 27). These two examples illustrate a case in which inputs with different sources of variation were incorporated in the analysis.

Response 36

Contact rate is a source of uncertainty rather than variability in the model. Contact rate is a parameter for transmission modeling that is fixed in the Markov Chain Reed-Frost approach used here. In the context of this modeling approach, the contact rate is a characteristic of the infectious agent (or reflects the agent-host-environment interaction).

The reviewer's assertion that a contact rate between 1 and 64 represents variability is not something that can be gleaned from the scientific literature. In fact, it is generally assumed that HPAI will behave similarly in any/all affected poultry flocks. What is uncertain (given the dearth of data) is exactly how it will behave.

Just as the author correctly identifies transition probabilities (*e.g.*, the conditional probability that an infected bird will die at 36 hours post-infection) as uncertain inputs to the model, the same can be said about the contact rate.

Comment 37

Thus, it is the case that the authors commingled these two concepts in their analysis and did not differentiate between variability and uncertainty. As a matter of fact, the reviewer believes that combinatorial analysis cannot separate between different sources of variation in the model, and hence, it is not applicable when model parameters hold both variability and uncertainty in their values.

Response 37:

Although it is difficult to consistently separate variability and uncertainty in any risk assessment, we have tried to do so throughout this analysis. As noted previously, our contention is that each calculation of the model represents variability.

Comment 38

As an alternative to combinatorial analysis, the reviewer still suggest using Monte Carlo simulation using the best data available for forming the probability distributions of model parameters. This approach gives key advantages compared to combinatorial analysis: (a) variability and uncertainty in model parameters can be easily separated; and (b) extensive sensitivity analyses can be done to identify key sources of variability and uncertainty in the model. The authors may argue that there is not enough data to populate the model parameters, and hence, there will be substantial uncertainty when Monte Carlo simulation is used. However, as suggested by Nauta (2000), it may be better to imprecisely assign the input as uncertain and/or variable than not to separate them at all. Moreover, Mokhtari et al. (2006a) used bootstrap simulation and sensitivity analysis to quantify uncertainty in their risk assessment for *Salmonella* in egg-containing foods for a model that had limited data sources and numerous expert judgments for parameterizing the model inputs. This methodology can easily be adapted for HPAI risk assessment.

Briefly, Mokhtari et al. (2006a) discuss that the probability distributions of model inputs are typically based on analysis of available data. Thus, parameters of those distributions (e.g., geometric standard deviation of a lognormal distribution) are estimated using relatively small sets of sample data. Therefore, there is uncertainty in the estimates of these statistics. Such uncertainty can be quantified using classical statistical techniques or numerical simulation methods. Mokhtari et al. used bootstrap simulation to quantify uncertainty in their model assumptions. Bootstrap simulation is a numerical technique originally developed for the purpose of estimating confidence intervals for statistics (Efron and Tibshirani 1993). Typically, bootstrap simulations are repeated a number of times to evaluate numerical stability of the output distribution by comparing results among the multiple bootstrap simulations. Bootstrap simulation uses a conceptually straightforward approach. In the case of the HPAI model, a random sample, referred to as the "bootstrap sample," can be generated from each of the probability distributions developed or assumed for inputs. The maximum likelihood estimation (MLE) approach can be used to fit a probability distribution to each of the bootstrap samples. The parameters of the new distribution differ from those for the original distribution, representing uncertainty associated with the input assumptions. The number of bootstrap replications required depends upon the information needed. For example, to calculate the standard error of a statistic, Efron and Tabshirani (1993) suggest 200 or less bootstrap replications. However, for estimation of confidence intervals, more replication may be required.

Response 38

See Response 34. The model does attempt to separate uncertainty from variability.

Comment 39

Followed by bootstrap simulation of the model and in order to prioritize data collection activities, it is useful to identify the key sources of uncertainty. Because uncertainty results from lack of knowledge and specifically, as discussed by the authors in the Report, from lack of proper and representative data for factors affecting spread of HPAI in animals and food products, the collection of additional data is the only viable method for reducing uncertainty. In many cases, the uncertainty in the model output may be influenced by only a subset of the model inputs and their corresponding assumptions, also known as key sources of uncertainty. It would be an unwise allocation of scarce resources to spend an equal amount of effort collecting data and developing probability distributions for all model inputs, if the output is sensitive to only a small number of inputs. The key sources of uncertainty should be separately identified for the mean and different percentiles of risk distribution (e.g., 95^{th}, and 99^{th} percentiles). Sensitivity analysis can be performed to identify key sources of uncertainty for each of the selected statistics or percentiles. Application of sensitivity analysis to a case scenario using this type of probabilistic approach is informative for situations in which there is substantial uncertainty, especially regarding estimates of highly exposed individuals. A risk manager may prefer to make a choice of critical control point or critical limits taking into account uncertainty for a particular portion of the most exposed subpopulation. However, if time and resources permit, knowledge of key sources of uncertainty for the most exposed or at risk portion of the population can be used to prioritize additional data collection or research that could reduce uncertainty. The assessment can be revised based upon new information, and a decision could be made at a later time based upon the reduced uncertainties

Response 39

We agree with the reviewer that it is important to prioritize data needs. Ideally, one would want to collect data to fill gaps that are both highly uncertain and highly influential to model output. Again, though, 1) it is not necessary to use a Monte Carlo model to identify key sources of uncertainty and influence and 2) the model could be thought of as streamlined Monte Carlo simulation consisting only of discrete uniform distributions.

In looking just for sources of uncertainty and influence it may be more efficient to simulate two point distributions rather than the three point distributions we have used. This would involve setting upper and lower

bounds to inputs without regard to a central value. This interval analysis would identify best and worst case scenarios but would not give a central estimate of illness. This analysis would also simulate faster. Including all 13 uncertain inputs using three point distributions would result in 3^{13} ~ 1.6 million outputs. Including all 13 uncertain inputs using just two point distributions would result in 2^{13} ~ 8,192 outputs. See Section 6.3.

b. Review the available data and derived variables in conjunction with the underlying assumptions used in this risk assessment.

4) Have all key studies and data been identified? If not, the reviewer shall provide additional data sources and citations (where appropriate).

5) Have the data been correctly interpreted, analyzed, and used in the risk assessment? If not, the reviewer shall provide alternate interpretations, analysis, or suggested utilization of the data.

6) Please address the validity and appropriateness of all input data in the model.

Comment 40

This question is outside the area of the reviewer's expertise. However, in general the data sources are modest, largely derived from internal studies sponsored by various arms of USDA (FSIS and ARS), and mostly unpublished. It would, however, be unlikely that published work could be used to populate the risk assessment for HPAI model.

Response 40

No response necessary.

c. Review the complexity of the model. Is the model too complex or not complex enough to adequately address the risk management questions? Is the model over or under parameterized? State whether the model adequately characterizes the uncertainty present and whether variability has been addressed sufficiently. In areas where the reviewer identifies limitations, weakness, or inadequacies, the review shall provide alternate data, data analysis, and/or modeling approaches.

Comment 41

The reviewer believes that the model is not complex enough to adequately address the proposed risk management questions. The simplifying assumptions were such that they adversely affect the credibility of the results and the modeling approach. The limitations of the model with respect to general simulation methodology (i.e., combinatorial analysis) and also sensitivity and scenario analyses are discussed in the responses to the charge questions "*a*" and "*e*", respectively, and are not repeated here. However, the reviewer has concerns about two sections of the model and associated modeling approaches. These sections include the module for estimating within-flock prevalence and the egg preparation module. Current limitations are discussed in the following and alternative modeling approaches are suggested.

Response 41

> In general, there is insufficient data to populate the present model as fully as we would like. Increasing the complexity necessitates additional data which may not be available.

Comment 42

<u>Estimating within-flock prevalence for avian influenza</u>

The current model implements a simplified approach for transmission of AI within flocks of chicken and turkey. This simplified approach assumes that the simulation begins with a single infected bird with HPAI at a random time during rearing. This bird then becomes infectious and can spread the disease to neighboring birds. As the disease progresses, some birds will remain susceptible, some will become infected, some will proceed to being infectious, and others will die. A disease transmission model was developed to simulate the spread of disease within the flock once a single bird is infected. However, this approach is very simplistic and does not represent the actual process of within-flock transmission of HPAI.

Response 42

> The model uses one initially infected bird in the baseline scenario. It can, however, model many initially infected birds.

Comment 43

Within-flock prevalence (WFP) depends on the rate of transmission and is therefore is time-dependent for a positive flock. Although mathematical models have been previously used to investigate the pattern of disease epidemics in both human and animal populations (e.g., Baily 1975; Fukuda et al. 1984), poultry production is highly specialized and follows a defined structure that requires special attention to the pattern of

disease transmission when modeling an outbreak (ACMSF 1996). A model for transmission of *Campylobacter* within a flock of broiler chickens was developed by Hartnett et al. (2001) and discussed briefly in the following. This model can be adapted for current study and transmission of avian influenza. The model incorporates the social behavior of birds in a house as a major factor affecting within-flock transmission of infectious diseases.

Briefly, when the birds are one day old they are taken to a broiler-growing farm, where they remain until they reach slaughter weight at ages between 30 and 60 days to become table birds. At this point birds are removed from the house and transported to the slaughter facility for processing in order to produce the sale product. Upon arrival at the growing farms the birds are placed in a house where they form *spatial clusters* which is likely because of the social factors. This phenomenon has been investigated and well documented for fowls and birds in the commercial rearing environment (McBride et al 1962; Collias et al 1969; Preston and Murphey 1989). The area explored by a given bird diminishes with age, and hence, enhancing the clustering effect.

Although it is complex to model the mechanism by which a single bird becomes colonized or infected by HPAI and the time at which this occurs, it is reasonable to assume that transmission is initially confined to the cluster containing the first colonized bird. Thus, it is appropriate to model the process of flock colonization in two stages: (a) initial transmission within the cluster containing the first bird that is colonized (Stage 1); and (b) transmission through out the remainder of the flock (Stage 2). Methodologies for modeling each of these two stages are briefly discussed below. Authors are encouraged to review Hartnett et al. (2001) for further discussion.

Stage 1: Within-cluster transmission

The initial transmission can be described using a chain-binomial model of epidemic spread (Baily 1975; Jacquez 1987). Such a model is appropriate when the data available for parameter estimation are measured in discrete time as in the occurrence of infected birds with HPAI within the cluster containing the first positive bird. The basic chain binomial model describes the colonization of a random susceptible bird after a fixed constant time. The colonized bird is then removed from the susceptible population. New cases occur within the cluster in distinct groups at each time point, as described by the recurrence equation:

$$I_c(t+1) = I_c(t) + NI_c(t+1)$$

Where $I_c(t)$ is the number of colonized birds in the cluster at t and $NI_c(t+1)$ is the number of newly colonized birds in the period $(t, t+1]$ when $(t,t+1]$ or Δt can be defined as the latent time, i.e., time required by the virus to replicate before it can be shed and infect susceptible birds. The number of newly colonized birds at each time-point will follow a binomial distribution which depends upon the probability that a susceptible bird in the cluster becomes infected in time $(t, t+1]$, that is $p(t)$. The binomial likelihood for $NI_c(t+1)$ can be written as:

$$P[NI_c(t+1)=x_{t+1}, NI_c(t)=x_t,..., NI_c(1)=x_1 \mid I_c(0)=x_0] = \prod_i P[NI_c(i)=x_i \mid H(i-1)]$$

Where *H(t)* is the history of epidemic up to the selected point in time:

$$P[NI_c(t+1)=x_{t+1} \mid H(t)] = \begin{bmatrix} S_c(t) \\ x_{t+1} \end{bmatrix} \times p(t)^{x_{t+1}} \times [1-p(t)]^{S_c(t)-x_{t+1}}$$

$$H(t) = \{NI_c(t)=x_t, NI_c(t-1)=x_{t-1},..., NI_c(1)=x_1, I(0)=x_0\}$$

Where *S(t)* is the number of susceptible birds in the cluster at time *t*. When considering transmission of HPAI within a flock, the probability that a bird becomes colonized is dependent upon the transmission rate, the social need to make contact with other birds, and the probability of contact with a colonized bird. The key point when modeling transmission of HPAI within commercial flocks is the flock size and hence lack of validity for random mixing as a reasonable assumption. In order to model the transmission process, the following assumptions can be made:

(i) the total cluster size remains constant, i.e., $S_c(t)+I_c(t)=n_c$ for all values of t where n_c is the total cluster size;
(ii) a bird, which becomes colonized at time t cannot transmit the organisms to another bird until time t+1 which allows for a fixed latent period
(iii) birds within the cluster act independently
(iv) each non-colonized bird has the same probability of being colonized at time t

From the work of Ng and Orav (1990) and with an assumption of independence for individual birds, the probability that a susceptible bird becomes colonized in the period (t, t+1], *p(t)*, can be estimated by:

$$p(t) = 1 - \left[1 - P_c\left(\frac{I_c(t)}{n_c}\right)\left(\frac{1-\exp(-y \times b)}{1-\exp(-y)}\right)\right]^{n_c}$$

In above equation, b represents the probability of transmission given a single contact of a susceptible bird with a colonized bird, P_c is the probability that contact is made with another bird, and y is the mean number of times contact is made with each bird. We should note that the number of contacts is limited to be equal to or less than the cluster size, but the number of times contact is made is theoretically unbounded. The mean number of newly colonized birds is then given by:

$$NI_c(t+1) = p(t) \times S_c(t)$$

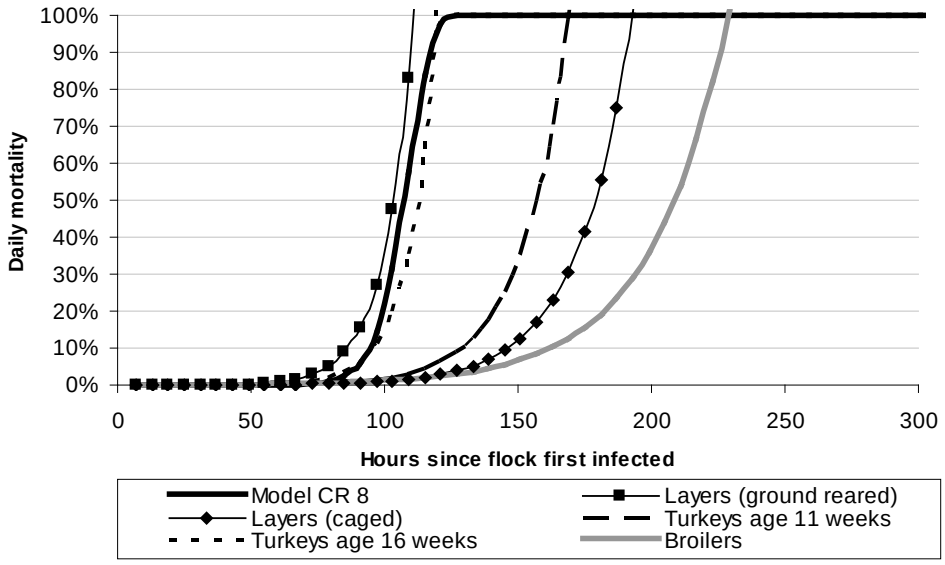
Response 43

Although a plethora of mathematical models are available for describing transmission of infectious agents among poultry populations, we chose to use a simple state-transition Markov chain model that is augmented with a Reed-Frost transmission assumption. The mathematics of this model are based on binomial probabilities in a manner similar to the model proposed by the reviewer. These mathematics are now explained in Appendix C.

Given the objectives of this analysis, the scope of transmission modeling employed was sufficient. Although it might be interesting to compare predictions across alternative models, there is no reason to believe a priori that any differences will substantially alter our model's conclusions.

Our choice of a state-transition Markov chain model and Reed-Frost assumptions was based on the limited data currently available. Clustered transmission among a flock of birds may, in fact, occur, but the available data do not include the spatial details necessary to validate a clustered occurrence of infection. Future models of HPAI transmission may address such spatial clustering patterns if better data become available.

We believe the transmission model we've employed is sufficiently robust for the objectives of this analysis. The state-transition Markov chain model and Reed-Frost assumptions are common approaches suggested in standard veterinary epidemiology texts. The predictions of our model closely match the current data of ground reared birds; the fit of the model's predictions to the data from Elbers et al., (2007) is illustrated in the figure below.



The following text has been added to the report: "To help validate this assumption [contact rate of 8 for ground-reared birds] using mortality as a surrogate for infection, data from Elbers et al., 2007 were considered. Within-flock mortality prevalence data from a total of 192 HPAI infected flocks were used to estimate regression coefficients by non-linear regression (Elbers et al., 2007). Mean estimated coefficients were used in the poultry transmission model to compare actual HPAI-infected flock data to model predictions at different contact rates. Figure 3 shows a contact rate of 8 and how it compares to the actual outbreak data. As can be seen, a contact rate of 8 represents the ground-reared layers and the turkeys aged greater than 16 weeks. Interestingly, the broiler data demonstrated a much slower spread of HPAI. These data are based from only 4 flocks and compared with 124 and 6 flocks for ground-reared layers and turkeys, respectively."

For cage-reared birds, see Section 4.5.1.2 and Response 210.

Comment 44

Stage 2: Epidemic spread

The colonization process in Stage 2 can be represented by the use of simple epidemic model. It can be assumed that in Stage 2 there is a flock of size *n*. The number of newly colonized birds is proportional to both the numbers of colonized and susceptible birds. Therefor, the process can be described typical by differential equations and solution to the process for the number of susceptible can be given as:

$$S_B(t') = \frac{S_B(t^*)n}{S_B(t^*) + I_c(t^*)\exp[nb_B t']}$$

Where, *b* is the transmission probability in the second stage which may or may not be equal to *b*, *t'* is equal to $t - t^*$, and t^* is the threshold time required for Stage 2 to start after introducing a single infected bird into the flock. After completion of the first and second stages the total number of colonized birds within a flock *I(t)* is given by:

$$I(t) = n - S_B(t)$$

Therefore, the within-flock prevalence at time *t* since the time of introducing a single infected bird into the flock can be estimated as:

$$P_{wfp}(t) = \frac{I(t)}{n}$$

Response 44

See Response 43.

Comment 45

Egg preparation module

The egg production birds were modeled in a similar manner as meat birds in that both used the transmission model to estimate the within-flock prevalence of infected birds over time. The egg model consisted of three modules: production, processing, and preparation. Six cooking styles were considered in the model including soft boiled and poached, sunny side up, scrambled and omelets, over easy, hard boiled, beverages, and mixtures. The preparation module estimated human exposure to HPAI based on the number of servings consumed, viral level per serving, and the effect of cooking (and pasteurization) on reducing the amount of virus. However, there are a few limitations as far as modeling the consumer phase of the egg model. The egg model made several simplifying assumption among which include:

(a) prevalence of purchasing contaminated eggs by consumers was 100% when contaminated eggs from an infected flock reached the market
(b) each serving included one contaminated egg
(c) serving size was 60ml for all different cooking style
(d) no under-cooking was considered in the analysis
(e) egg-containing food products that include uncooked eggs (e.g., home made ice-cream and dressings) were not included in the model
(f) effect of pooling, i.e., breaking and mixing several eggs together was not considered

These assumptions are not representative of current egg preparation practice at consumer level and may overestimate or underestimate the magnitude of risk. Consumer preparation and handling may substantially impact the magnitude of risk. However, this factor was not included in the model. Mokhtari et al. (2006a) developed a risk assessment model for consumer-phase *Salmonella enterica* serotype Enteritidis in egg-containing food product incorporating alternative consumer food handling practices. The current food handling model for AI can be modified using the approach discussed in Mokhtari et al. (2006a). An overview of the suggested modeling approach with several adaptations for the AI risk assessment is given below.

Response 45

We agree with the reviewer that the egg model made simplifying assumptions regarding consumer handling and preparation, that they may or may not be representative of consumer practices, and that there are other models available. FSIS has developed risk assessment models for *Salmonella* Enteritidis which are much more complex than what is used for the HPAI model, but chose not to incorporate them.

There are substantive reasons for making the model as simple as possible:

1. The purpose of the egg model is not to determine risk to humans; rather, it is evaluate which combinations of events pose the most risk. It has a secondary purpose of informing regulatory decision makers about when recalls should be initiated and how far back in time to recall product.
2. Other aspects of the model (*e.g.,* dose response) are quite data poor, yet are even more important in determining risk. Devoting resources to the preparation and consumption part of the model will not help inform regulatory decision makers.

Furthermore, although modeling of consumer practices is kept simple, it is complex enough to demonstrate the substantial effect that cooking practices have on the possible exposure to HPAI.

Comment 46

Initial prevalence and contamination

To estimate the probability that an internally HPAI contaminated egg is used during meal preparation, first, the prevalence of internally contaminated shell eggs at home should be estimated. The prevalence of contaminated eggs reaching market can be estimated based on the total number of eggs produced by a flock within a time period of interest and the number of contaminated eggs. Next, the total number N of eggs used during meal preparation should be modeled. The distribution for the number of eggs used in a single serving is discussed in the next section. The probability that n HPAI contaminated eggs are selected for a single food preparation that includes N eggs can be modeled as a binomial distribution. The current model provides the level of HPAI per contaminated egg.

Consumer preparation and handling

In order to evaluate the impact of consumer preparation and handling on levels of HPAI in egg-containing foods, the foods can be classified into several categories representing combinations of three key preparation and handling behaviors, i.e., pooling of eggs, the use of the egg (as an egg dish or as an ingredient), and the degree of cooking. These three consumer behaviors have been shown to impact the final number of Salmonella cells in the food at consumption (Health Canada 2000), and hence, are expected to similarly impact the number of HPAI viruses in egg-containing foods. Suggested categories may include: (1) fried eggs; (2) soft-boiled, hard-boiled, poached eggs; (3) scrambled eggs and omelets; and (4) ice-cream and dressings.

Response 46

Although this model does not include pooling it does simulate six different types of preparation: soft boiled and poached, sunny side up, scrambled and omelets, over easy, hard boiled, beverages, and mixtures. Each of these categories is represented with a fixed log reduction. Pooling was not incorporated into the model because 1) it added unnecessary complexity and 2) it would not have been helpful in answering the risk management questions.

Comment 47

More eggs become contaminated when non-contaminated and contaminated eggs are pooled. Pooling can be assumed for foods in Categories 3 and 4, e.g., scrambled eggs and in foods for which eggs were used as an ingredient, e.g., ice cream and dressing. The number of eggs pooled for a single food preparation event can be modeled using a discrete distribution as:

$$n_{eggs} = \text{Discrete}(n, p)$$

Category 3: $n = \{1, 2, 3, 4, 5, 6, 7, 8\}$; $p = \{0.09, 0.17, 0.21, 0.20, 0.15, 0.09, 0.05, 0.02\}$
Categories 4: $n = \{1, 2, 3, 4, 5, 6, 7\}$; $p = \{0.13, 0.21, 0.23, 0.19, 0.12, 0.07, 0.03\}$

The parameters of this distribution are based on the data provided in Mokhtari et al. (2006a). It can be assumed that only one egg is used for Categories 1 and 2. For the cooking step, three possibilities should be modeled: thorough cooking, under-cooking, and no cooking. Mokhtari et al. (2006a) provided data for frequency of each of these cooking practices. For example, the percentage of consumers who practice thorough cooking were 51%, 83%, 98%, and 73% for Categories 1 to 4, respectively. The proportion of undercooked eggs for these categories is 100% minus the thorough cooked proportions; however, for Category 4, 26% of consumers were identified to use uncooked eggs, and hence, 1% used undercooked eggs. No cooking effect should be considered for uncooked eggs that are used directly or as an ingredient in egg-containing food products.

Response 47

As noted above (Response 46), we chose to not model egg pooling as we did not deem it helpful in answering risk management questions. We did model different levels of cooking effectiveness by assigning eggs to different cooking scenarios.

d. Evaluate the risk assessment model source code and mathematics.

1) ***Are the modeling techniques (model mathematics and equations) appropriate? If not, the reviewer shall provide alternate modeling techniques.***

2) ***Are the methodologies used in the risk assessment for estimating parameters from the data appropriate (i.e., follow scientifically accepted methodologies)? If not, the reviewer shall provide an alternate approach.***

Comment 48

There are key limitations with respect to the modeling techniques that are fully discussed in responses to the charge questions "*a*" and "*c*". These limitations are not repeated here.

3) ***The reviewer should examine and verify that the data analysis and source code are accurate.***

The reviewer's main concern is the lack of transparency of the source code. Very few informative comments are given within the visual basic code or inside Microsoft Excel worksheets. Thus, it was a tedious task to understand the modeling flow and connection between different cells in each worksheet. It was also not possible to understand some sections of the model. For example, the reviewer found the "TransmissionModel" worksheet very confusing. Because most of the modeling structure is in the form of embedded equations inside different cells, it was not practical or even possible to verify that the model had been accurately coded. However, the reviewer was able to execute the code and generate similar results as those given in the Report.

Response 48

The model is written entirely in Excel. The auditing toolbar allows one to trace all precedent and dependent cells to any cell in the workbook. The addition of a mathematical annex based on the Excel workbook should make future audits easier (See Appendix C).

Visual Basic for Applications is used to perform the combinatorial evaluations for different scenarios. It is not an intrinsic part of the model in that its only use is to replace different inputs and recalculate. In this way it operates much like a standard Monte Carlo modeling package (*e.g.*, @Risk) for evaluating the effect of uncertainty.

e. ***Evaluate whether adequate sensitivity analysis has been provided. Have the most important variables in the model been identified? Has an important variable been left out? Has the impact of including or excluding scientific studies or other data been adequately explored? If so, the reviewer shall provide an alternate approach or application for sensitivity analysis and/or identify those parameters that should have been included***.

Comment 49

Reviewer believes limited and inadequate sensitivity analysis was performed. The methodology used for sensitivity analysis is based on changing values of individual model inputs, one at a time, while holding other inputs at their mean or baseline values (this is not clearly specified in the Report). The authors subsequently measured the impact of these changes on the risk estimates. Results from these sensitivity or so called scenario analyses are given in Figures 11 to 18 in the Report. The authors compared the importance of model parameters based on the magnitude of their impact on the risk estimates. For example, varying the number of meat-type birds from 1 to 10,000 showed a two fold effect on the risk estimates (Page 80), while varying the contact rate from 1 to 64 resulted in an approximate 9 fold difference compared with a 26 fold difference for egg and poultry consumption, respectively (Page 82). This methodology for sensitivity or scenario analyses has significant shortcomings: (a) it fails to consider possible interactions between model parameters and nonlinearity in model structure; (b) individual impacts of model parameters cannot be compared as indices for sensitivity; and (c) impacts from uncertainty and/or variability in model parameters were misleadingly commingled. The latter shortcoming is because the authors did not try to separate variability and uncertainty in model parameters. This issue is further discussed in response to the charge question *a* and is not repeated here.

Response 49

We agree with the reviewer that this method of sensitivity analysis has shortcomings and therefore have developed a sensitivity analysis using the combinatorial approach. Because all parameters are run at the same time, this type of sensitivity analysis addresses the reviewers primary concern that interactions between model parameters were not addressed previously (see Section 6.3.1).

The separation of variability and uncertainty is discussed in Response 34.

Comment 50

Mokhtari and Frey (2005a) recently presented a comparison of the capabilities of various sensitivity analysis methods with regard to both the characteristics of the model and the analytic objectives. Whereas some methods were based on the local perturbations of inputs, others were based on results from Monte Carlo simulations. A key conclusion from that work was that methods based on the local perturbations of inputs (similar to the approach used in this analysis) and those conventionally used for sensitivity analysis and available in commercial statistical software packages (e.g., correlation analysis) may not provide robust results when applied to risk assessment models, and hence, should be carefully used, if at all, for sensitivity analysis. However, based on their recommendation example of promising sensitivity analysis methods include categorical and regression

trees (Mokhtari et al. 2006b), analysis of variance (Mokhtari and Frey 2005b), and Sobol's method (Mokhtari et al. 2006c). These methods are model-independent, and hence, are preferred over model-dependent techniques. Thus, such methods should be the starting point for this analysis. However, the key criterion for application of these techniques is using Monte Carlo simulation to propagate distributions of model parameters. Suggestions for using Monte Carlo simulation instead of combinatorial analysis is given in response to the charge question *a* and is not repeated here.

Response 50

See Response 34.

f. Comment on the adequacy of the risk assessment model documentation. Is the report clearly written? Is it complete? Does it follow a logical structure and layout? Is it useful? If not, the reviewer shall provide an alternate outline and/or approach for adequately and clearly documenting this risk assessment.

Comment 51

Unfortunately, the authors failed to present the structure of the model in sufficient detail. Thought out the report, no equation was given for any part of the modeling structure. For example, on Page 35 and it is discussed that a transmission model has been developed to simulate the number of birds within a flock considering four different stages of susceptibility, latent, infectious, and death. However, it was not clear for the reviewer how this task has been done. Since it was difficult to understand the structure of the model from the information provided in the Report, the reviewer was forced to refer to Excel worksheets and the visual basic code for this purpose. There is no specific discussion of the modeling approach in Excel sheets or the visual basic code either. It was clear to the reviewer that the available code was not provided for a practical second-person review, and could only be understood by the original developers. Perhaps, if the reviewer had substantial amount of time to examine the computer code (Excel sheets), he could understand the model structure and the flow of the data information in the model better; however, a better approach would be to make the structure of the model clear in the documentation with further illustrative examples given with respect to the step-by-step execution of the model and a list of key model equations.

Response 51

An appendix has been added that describes the mathematical basis of the model (see Appendix C).

Comment 52

As discussed above, the authors chose Microsoft Excel using visual basic macro programming, which results in a black box model that cannot be easily checked for programming errors. The huge number of parameters and equations included in the analysis are embedded within cells in different Excel worksheets and within many data tables. Thus, it is difficult to understand the flow of the model and the connection between different cells and tables inside alternative worksheets without clear knowledge about the modeling approach. As an alternative, the modeling should be more transparent, specifically to prevent users inadvertently making changes that result from the inability to see every detail of the programming. Furthermore, it would be beneficial to provide sufficient comments within worksheets and also the code to facilitate understanding of the modeling flow. One suggestion is to use a programming environment rather than using embedded equations in Microsoft Excel. The choice of programming environments depends on the skill of the modeler, the use of add-ins, and the scope of the analysis. For models that are extensive and that will be used for multiple analyses, a programming language environment and good software engineering practices are recommended. The choice of modeling environment should account for the trade-off, if any, between the skills of the analyst, resources, anticipated needs for future model refinements, and desired flexibility with regard to sensitivity analysis. Unfortunately, the current model substantially lacked good software engineering practice.

Response 52

As noted, a mathematical annex has been added to the documentation (see Appendix C). This documentation makes the implementation of the model less relevant as similar results should be able to be obtained with other platforms.

The model was developed in Excel which has the advantages of ease of use and a broad user base. Another advantage is the ability to use formula auditing which lets a user see exactly which inputs are used in cells and what cells are dependent on those.

Although Visual Basic for Applications was used to facilitate the scenario analysis it was used not used to generate calculations for any specific iteration. There is thus no need to look at any of the code to see how the model works.

g. Evaluate the approach taken to estimate illnesses due to consumption of HPAI. Does the data derived from the animal model provide a sufficient surrogate upon which to estimate human illnesses? Are there additional methods to better utilize these or other data? If so, what additional approach should be taken?

Comment 53

Answering the question regarding the suitability of data used for dose-response characterization is outside the area of the reviewer's expertise.

Response 53

No response necessary.

References

ACMSF. 1996. Advisery Committee on the Microbiological Safety of Food. Report on Poultry Meat. London: HMSO.

Anderson EL, and Hattis DH. 1999. When and how can you specify a probability distribution when you don't know much? Risk Anal 19(1): 43-68.

Bailey, NTJ. 1975. The Mathematical Theory of Infectious Diseases and its Applications. Great Britain: Charles Griffin and Company.

Collias N.E., Collias E.C., Hunsaker D., and Minning L. 1966. Locality fixation, mobility and social organization within an unconfined population of Red Jungle Fowl. *Animal Behaviors* 14: 550-559.

Cullen AC, and Frey HC. 1999. Probabilistic Techniques in Exposure Assessment. Plenum Press, New York, USA.

Efron B., and Tibshirani R.J. An Introduction to the Bootstrap. Chapman and Hall, New York, 1993.

Fukuduka K., Sugawa K., Ishii K. 1984. Simulation of infectious disease by Reed-Frost model with proportion of immune and innaparent infection. *Computers in Biology and Medicine* 14: 209-215.

Hartnett E., Newell K.D., Wooldridge M., and Gettinby G. 2001. A quantitative risk assessment for the occurrence of campylobacter in chickens at the point of slaughter. *Epidemiology and Infection,* 127: 195-206.

Health Canada. 2000. Risk assessment model for *Salmonella* Enteritidis. Unpublished Health Canada Document.

Jacquez J.A. 1987. Note on chain-binomial models of epidemic spread: what is wrong with the Reed-Frost formulation? *Mathematical Biosciences* 87: 73-82.

McBride G., and Foenander F. 1962. Territorial behaviors in flocks of domestic fowls. *Nature 192: 102.*

Mokhtari, A., and H.C. Frey. 2005a. Recommended practice regarding selection of sensitivity analysis methods applied to food safety risk process models. *Human and Ecological Risk Assessment 11*(3):591–605.

Mokhtari, A., and H.C. Frey. 2005b. Sensitivity analysis of a two-dimensional probabilistic risk assessment model using analysis of variance. *Risk Analysis 25*(6):1511–1529.

Mokhtari, A., C. Moore, H. Yang, L. Jaykus, R. Morales, S.C. Cates, and P. Cowen. 2006a. Risk assessment for salmonellosis associated with egg preparation at home. *Risk Analysis 26*(3): 753–768.

Mokhtari, A., H.C. Frey, and L. Jaykus. 2006b. Evaluation of classification and regression trees for sensitivity analysis: case study for the *E. coli* food safety risk assessment model. *Journal of Food Protection 69*(3):609–618.

Mokhtari, A., H.C. Frey, and J. Zheng. 2006c. Evaluation and recommendation of sensitivity analysis methods for application to EPA-Stochastic Human Exposure and Dose Simulation (SHEDS) models. *Journal of Exposure Science and Environmental Epidemiology* 16(6): 491-506.

Murphy BL. 1998. Dealing with uncertainty in risk assessment. *Human and Ecological Risk Assessment* 4(3): 685-699.

Nauta MJ. 2000. Separation of uncertainty and variability in quantitative microbial risk assessment models. *International Journal of Food Microbiology* 57(1): 9-18.
Ng J., and Orav E.J. 1990. A generalized chain-binomial model with application to HIV infection. *Mathematical Biosciences* 101: 99-119.

Preston A.P., and Murphy L.B. 1989. Movement of broiler chickens reared in commercial conditions. *British Poultry Science* 30: 519-532.

6 REVIEWER NUMBER 3

Comment 54

Avian influenza and the food chain

1. There is a theoretical risk that AI strains could enter the human food chain, but this risk is low, and no risk has been defined in studies of human AI outbreaks.

Response 54

This comment and the following four comments appear to be taken verbatim from the qualitative risk assessment Advisory Committee on the Microbiological Safety of Food, 2005. Avian Influenza Risk Assessment – Update November 2005, Discussion Paper. ACM/768. The interagency risk assessment quantifies the risk associated with HPAI entering the food supply and agrees that the risk is "low".

Comment 55

2. The risk of high pathogenicity strains entering the food chain is likely to be contained, because clinically affected poultry will be excluded from slaughter as a result of pre-slaughter veterinary checks. Thus, the only exposure in poultry meat should be to low pathogenicity AI viruses.

Response 55

The risk assessment demonstrates that there are combinations that could result in contaminated poultry meat entering the food supply. The comment appears to assume that there will be enough time for infected poultry to be excluded.

Comment 56

3. Low pathogenicity AI viruses are confined to the intestinal tract in poultry, and will not replicate after slaughter. Consequently, there is a low risk of contamination of chicken carcasses with AI, which could lead to exposure of individuals involved in food handling and preparation.

Response 56

LPAI is outside of the scope of this risk assessment.

Comment 57

4. In May 2003, highly pathogenic H5N1 was isolated from duck meat imported from China to Japan. Highly pathogenic AI strains usually cause no symptoms in water birds, so an AI infection may not be diagnosed.

Response 57

HPAI contaminated duck meat is outside of the scope of this risk assessment. There is a brief discussion of HPAI contaminated duck meat entering the food supply in the risk assessment (see Section 4.6.1).

Comment 58

5. Proper cooking will destroy any virus present in meat or eggs. Moreover, non-specific defenses, such as saliva or gastric acid, provide a primary barrier against infection following ingestion of viruses.

Response 58

The risk assessment evaluates the impact of improper cooking as consumers can undercook poultry and eggs. The risk assessment does not evaluate the potential impact of "non-specific defenses, such as saliva or gastric acid" as data were not identified to quantitatively measure the impact. Additional data were not provided by the reviewer.

Comment 59

Conclusions

- **The scope of this risk assessment primarily considered direct foodborne exposure of humans from consumption of contaminated poultry, shell eggs, and egg products. This assessment did not address indirect food exposures, such as occupational exposure during poultry processing or retail or home food preparers that could be exposed to HPAI during preparation.**

- **This risk assessment described a comprehensive data-driven, systems analysis approach that collated available data, incorporated them into a mathematical**

model for the various variables. It may provide risk managers with a decision-support tool to evaluate the effectiveness of current and future interventions in reducing foodborne illness from HPAI in the U.S.

Response 59

This comment appears to be taken verbatim from the risk assessment report Risk Assessment for the Public Health Impact of Highly Pathogenic Avian Influenza Virus in Poultry, Shell Eggs, and Egg Products, 3/14/07.

Comment 60

- **The present risk assessment report did not include ducks or duck meat although this fowl species is commercially produced in significant numbers in certain facilities in the US and is exported widely**. (Maple Leaf Farms, Northern Indiana).

Response 60

The reviewer's comment is appreciated. This risk assessment, as well as others, (Advisory Committee on the Microbiological Safety of Food, 2005; French Agency for Medical Safety of Food, 2005) qualitatively addresses HPAI contaminated ducks (see Section 4.6.1). The risk assessment report also states that "…ducks and geese constitute approximately 0.3% of the total poultry production mass slaughtered in FSIS inspected plants (eADRS, 2002)." It is unclear if the reviewer does not agree that ducks constitute a small fraction of FSIS regulated bird processing plants. Nevertheless, additional data are not provided.

Comment 61

The followings may summarize the conclusions of the report that are consistent with the findings and conclusions of the most recent WHO/FAO Advisory Committee on the Microbiological Safety of food (ACMSF) Avian Influenza Risk Assessment reports on the risk assessment of HPAI in food chains (2005).

- **AI outbreaks in humans in recent years have shown that there is no absolute species barrier between humans and birds.**

- **Evidence from recent outbreaks indicates that direct contact with infected birds is the main risk factor for human infections, and that consumption of infected chickens has not been identified as a risk factor.**

- **Limited studies of AI infections in occupationally exposed groups, and general population studies, have failed to identify significant unrecognized human AI infection.**

- **Several factors will contribute to preventing or limiting infection following ingestion of viruses, including lack of appropriate receptors, and nonspecific defenses such as saliva or gastric acid. Proper cooking will destroy any virus present in meat or eggs.**

- **In the U.S., HPAI H5N1 has not been detected in wild birds or other avian species, and therefore, risk of contracting HPAI from ingestion of processed poultry, shell eggs and egg products is very low (WHO, 2006d). Other subtypes of HPAI have been detected in the U.S. as recently as 2004 (USDA, 2006).**

The risk of acquiring AI through the food chain is low, and there is no direct evidence to support this route of infection. However, more studies of the factors affecting human infection, and studies of occupationally exposed groups, should be encouraged.

Response 61

Conclusions are taken primarily and in some instances verbatim from the qualitative risk assessment "Advisory Committee on the Microbiological Safety of food, 2005. Avian Influenza Risk Assessment – Update November 2005, Discussion Paper. ACM/768".

Comment 62

Below, are the comments of the reviewer to the specific questions that were requested in the document of reviewers charge:

a. Is the overall approach for modeling the risk of HPAI from consumption of HPAI-contaminated poultry, shell eggs, and egg products, as described in the report, fundamentally sound?

Yes, appropriate

Response 62

No response necessary.

Comment 63

• Specifically, is the use of a combination of scenarios, given the availability of data, as opposed to a probabilistic approach, appropriate?

Use of combination of scenarios may be more appropriate than the probabilistic Monte Carlo analysis due to lack of quantitative data to properly characterize the variability within each model variable. It is unclear how accurately some of the data identified represent the true range of values from the HPAI natural system. Therefore, the combinatorial analysis allows evaluation of many different scenarios with a range of data inputs for each important parameter allowing users to evaluate the effect of each parameter and its accompanying uncertainty on the estimated number of human illnesses due to consumption of poultry or eggs from HPAI infected flocks, resulting from the respective exposure pathways that comprise several stages; (production, processing, preparation, and dose-response).

• Does the combinatorial approach adequately answer the risk management questions and would these models be useful in guiding and prioritizing emergency and preventive measures, and guiding risk communication messages should HPAI be detected in the U.S.?

If not, what problems exist and how should they be addressed?

The combinatorial analysis allows evaluation of many different scenarios with a range of data inputs for each important parameter.
The advantage of this approach is that it can test several scenarios and can examine the sensitivity of the output to each of the input parameters and how important is each parameter for the exposure level of humans to HPAI through consumption of poultry or eggs.

Response 63

No response necessary.

Comment 64

Guiding and prioritizing emergency and preventive measures, and guiding risk communication messages should HPAI be detected in the U.S. May not be optimal.

For guiding and prioritizing emergency and preventive measures, and guiding risk communication messages should HPAI be detected in the U.S., the study may not be adequate due to the lack of sufficient scientific studies to determine HPAI transmission and pathology parameters within an environment that accurately represents a U.S. commercial poultry house and due to the lacking of significant database on the poultry product association with human infection with HPAI.

Needs: Inclusion in the analysis, of most recent data on human infections with HPAI suspected to have been resulted from consumption of poultry and poultry products or cases with no ascertainment of the exposure risks particularly from South East Asia (Indonesia) and through encouragement for sharing such information by authorities in areas where such cases are frequently reported.

Response 64

The reviewer's comment is appreciated and highlights the impact that lack of robust data can have on a risk assessment. The reviewer suggests that inclusion of additional data from outbreak studies could be useful. Certainly, if such data exist, this would help to further inform the model. Unfortunately, the reviewer does not provide references or contact information to begin to explore if such data exist and to date it is our understanding that consumption as an exposure pathway has not been fully documented.

Comment 65

B. REVIEW THE AVAILABLE DATA AND DERIVED VARIABLES IN CONJUNCTION WITH THE UNDERLYING ASSUMPTIONS USED IN THIS RISK ASSESSMENT.

1) Have all key studies and data been identified? If not, the reviewer shall provide additional data sources and citations (where appropriate).

Yes

2) Have the data been correctly interpreted, analyzed, and used in the risk assessment? If not, the reviewer shall provide alternate interpretations, analysis, or suggested utilization of the data.

Yes

Data were correctly interpreted and used in the risk assessment analysis.

3) Please address the validity and appropriateness of all input data in the model.
Valid and appropriate.

c. Review the complexity of the model. Is the model too complex or not complex enough to adequately address the risk management questions?

a. Is the model over or under parameterized?

State whether the model adequately characterizes the uncertainty present and whether variability has been addressed sufficiently. In areas where the reviewer identifies

limitations, weakness, or inadequacies, the review shall provide alternate data, data analysis, and/or modeling approaches.

Due to the uncertainty of the data, the baseline predicted human illness of 795, 1,214, and 90 for chicken, turkey, and hen flocks respectively could range from < 1 to > 6000 illnesses which id quite broad range. However, the purpose of the model is not to predict the absolute number of illnesses, especially given that further research, which listed in the report, is needed.

d. Evaluate the risk assessment model source code and mathematics.

7) Are the modeling techniques (model mathematics and equations) appropriate? If not, the reviewer shall provide alternate modeling techniques.

Modeling techniques appear appropriates for the selected approach.

8) Are the methodologies used in the risk assessment for estimating parameters from the data appropriate (*i.e.*, follow scientifically accepted methodologies)? If not, the reviewer shall provide an alternate approach.

Methodologies that were used in the risk assessment to estimate parameters from the data are appropriate.

9) The reviewer should examine and verify that the data analysis and source code are accurate.

Sources for this data-driven systems analysis approach that collated available data, their coding and the final incorporation into a mathematical model sound accurate.

e. Evaluate whether adequate sensitivity analysis has been provided. Have the most important variables in the model been identified? Has an important variable been left out? Has the impact of including or excluding scientific studies or other data been adequately explored? If so, the reviewer shall provide an alternate approach or application for sensitivity analysis and/or identify those parameters that should have been included.

Adequate based on available data.

As listed in its 28 tables and 18 figures, the study report had identified and included most important variables related to the subject of this risk assessment in the model. The report does not seem to have overlooked important studies that could have been included and benefited the presented models.

f. Comment on the adequacy of the risk assessment model documentation. Is the report clearly written? Is it complete? Does it follow a logical structure and layout? Is it useful? If not, the reviewer shall provide an alternate outline and/or approach for adequately and clearly documenting this risk assessment.

Yes, to all.

Members of the team provided excellent documentation for the risk assessment model. Wrote very clear report that followed logical structure and layout. It is useful in clarifying the risk, based on the current knowledge on the microbiology and epidemiology of the

potential types and strains of HPAI viruses that were most commonly reported among humans from SE East Asia. It suggests that the current risk associated with consumption of poultry and poultry products that may be contaminated with the HPAI virus, is rather low.

Response 65

No response necessary.

Comment 66

Evaluate the approach taken to estimate illnesses due to consumption of HPAI. Does the data derived from the animal model provide a sufficient surrogate upon which to estimate human illnesses? Are there additional methods to better utilize these or other data? If so, what additional approach should be taken?
May not be optimal.
Due to the lack of significant database on the illness that might have resulted from consumption of poultry and poultry products contaminated with the HPAI viruses and the uncertainty of person to person transmission of the HPAI viruses, one must conclude that the adequacy of the conclusion based on data from animal models may not be sufficient.
Needs: continuous collection of data on significant cases of HPAI viruses that suggest a role for food consumption in the etiology of the HPAI in humans.

Response 66

Collection of epidemiological data related to human HPAI consumption is outside of FSIS' mission. However, the reviewer makes note that the current does-response model may not be appropriate. In response to this, we have used the data from an AI human intranasal study to develop an alternative dose-response for consumption of HPAI (see Section 5.1). In addition, we are in the process of acquiring data from ARS regarding their mammal feeding trial.

7 REVIEWER NUMBER 4

Comment 67

a. Is the overall approach for modeling the risk of HPAI from consumption of HPAI-contaminated poultry, shell eggs, and egg products, as described in the report, fundamentally sound? Specifically, is the use of a combination of scenarios, given the availability of data, as opposed to a probabilistic approach, appropriate? Does the combinatorial approach adequately answer the risk management questions and would these models be useful in guiding and prioritizing emergency and preventive measures, and guiding risk communication messages should HPAI be detected in the U.S.? If not, what problems exist and how should they be addressed?

The overall approach appears to be sound. The use of a combination of scenarios vs. a probabilistic approach is appropriate, given the data available. The combinatorial approach appears to adequately answer the risk management questions. These models would be quite useful in guiding and prioritizing emergency and preventive measures. They would also be of some use in guiding risk communication messages (i.e. If you cook your chicken to 155 you will be safe, don't eat undercooked eggs, etc.

b. Review the available data and derived variables in conjunction with the underlying assumptions used in this risk assessment.

The data and derived variables appear to be consistent with the assumptions, except as noted.

1) Have all key studies and data been identified? If not, the reviewer shall provide additional data sources and citations (where appropriate).

The team has done a very nice job is assembling all the relevant research on this topic, as well as collecting expert opinion where available.

2) Have the data been correctly interpreted, analyzed, and used in the risk assessment? If not, the reviewer shall provide alternate interpretations, analysis, or suggested utilization of the data.

Except as noted in my detailed, page by page comments (see below) the data have been correctly analyzed and interpreted.

2) Please address the validity and appropriateness of all input data in the model.

All input data appear to be valid and appropriate, except as noted below.

Response 67

No response necessary.

Comment 68

c. Review the complexity of the model. Is the model too complex or not complex enough to adequately address the risk management questions? Is the model over or under parameterized? State whether the model adequately characterizes the uncertainty present and whether variability has been addressed sufficiently. In areas where the reviewer identifies limitations, weakness, or inadequacies, the review shall provide alternate data, data analysis, and/or modeling approaches.

The model appears to be complex enough to adequately address the risk management questions. The Excel spreadsheets are quite complex, and although the modelers have done a good job laying everything out and clearly labeling everything, the spreadsheets would benefit from additional explanatory text. Ideally, a "users manual" should be provided that would explain where the user can make inputs, and where to look for outputs.

Response 68

The reviewer appropriately notes that guidance for using both the poultry and egg model were missing at the time of the review. A "user's manual" has been provided as Appendix A to the main report.

Comment 69

The model appears to be adequately parameterized. As noted in my detailed comments below, it might be interesting (but not essential – especially if the authors can justify the choice) to look at the choice of the 6 hours window, and see what difference a 4 or 8 hour window would make.

Response 69

See Response 158.

Comment 70

The model appears to adequately characterize the uncertainty and variability present.

d. Evaluate the risk assessment model source code and mathematics.

I did find what appears to be a superficial error in the SummaryModelResults tab for the Poultry model. When the birds initially infected variable is changed to include 1 and 10,

the SummaryModelResults tab only shows values of "1" for each iteration. Note that answers appear to be correct, but the input cell data (column I) s wrong, and only shows 1's, even when it should shows 1's and 10's. Note that the same bug also manifests in the egg model.

Response 70

The reviewer is correct that there was an error with the SummaryModelResults for this particular input. The error has been corrected and the other model inputs have been checked.

Comment 71

As noted above, a user's manual would aid in understanding and using a model. For example, in the "SummaryModel" tab of the meat model, cell B11, it says "Infectiousness to birds (which option to model)", and spreadsheet I was sent says "19". There is no way to easily see what "option 19" means, or even what other options might be available, without searching through the entire spreadsheet. Interestingly, I was able to find the information I was looking for in Appendix A, but not in the spreadsheet. For some reason a text search on "Infectiousness to birds" will not find the text string in cell B2 of the ModelOptions tab! It would be a simple matter to add a hypertext link from a cell near the descriptor, to link to this location in the spreadsheet.

Response 71

Reviewer's comments have been addressed in Appendix A.

Comment 72

I would also suggest that the macro code be commented. Although the programmer has done a good job using clear parameter names, the code itself is uncommented, and hence not terribly understandable without a great deal of study - which would exceed the time and budget provided for review.

Response 72

Some commentary has been added to the macro code.

Comment 73

Another minor point regarding consistency between the two models: For the meat model the "Threshold for mortality (on farm)" values are percentages (i.e. 2%) and the spreadsheet inputs are integers, so the user would input "2" for 2%. Conversely, in the egg model, the user types is "0.02" for a value of 2%. If the user types in a value of "2" in the egg model (essentially 200%, which means the mortality value is never reached) the number of expected illnesses is very large because the simulated flock continues to produce contaminated eggs until the entire flock expires.

Response 73

The reviewer is correct. To address this, a suer's manual has been developed (Appendix A). The following table is part of the user's manual. Row 13 (model parameter 12) shows that the model input for eggs is a fraction ranging from 0 to 1.

	Egg Model Variable	Input range	Hen Baseline inputs
1	*In-shell pasteurization*	0 – 10 $\log_{10}$	0
2	*Flock size*	100-1,000,000 birds	100,000
3	*Contact rate*	1 - 64	2
4	*Infectiousness to birds*	Option 1-23	19
5	*Tissue infectivity (whether eggs are contaminated)*	Option 1-6	1
6	*Mortality of birds*	Option 1-8	1
7	*Dose response (r-value for exponential function)*	10^{0} – 10^{-12}	0. 000000433
8	*Levels of EID50s in eggs*	Option 1-3	1
9	*% of eggs showing pathology*	Option 1-3	1
10	*Birds initially infected*	1 - # birds in house	1
11	*Cooking scenario*	Option 1-6	2
12	*On farm mortality detection threshold*	0.00 – 1.00	0.02
13	*Egg contamination*	Option 1-3	1
14	*Days eggs held before marketing*	0 – 10 days	2
15	*Threshold for egg contamination (only when option 3 for input 13 is modeled)*	0 - 48 hours	18

Comment 74

1) Are the modeling techniques (model mathematics and equations) appropriate? If not, the reviewer shall provide alternate modeling techniques.

The modeling techniques appear to be appropriate.

2) Are the methodologies used in the risk assessment for estimating parameters from the data appropriate (i.e., follow scientifically

accepted methodologies)? If not, the reviewer shall provide an alternate approach.

The methodologies used in the risk assessment for estimating parameters from the data are generally appropriate.

3) The reviewer should examine and verify that the data analysis and source code are accurate.

The data analysis and source code appear to be accurate.

e. Evaluate whether adequate sensitivity analysis has been provided. Have the most important variables in the model been identified? Has an important variable been left out? Has the impact of including or excluding scientific studies or other data been adequately explored? If so, the reviewer shall provide an alternate approach or application for sensitivity analysis and/or identify those parameters that should have been included.

The modelers have done a good job looking at model sensitivity. It appears that the most important variables in the model have been identified. I could find no important variable that have been left out. Since the literature in this area is so sparse, there are few studies to exclude. The authors have done a good job collecting and analyzing what data are available.

Response 74

No response necessary.

Comment 75

f. Comment on the adequacy of the risk assessment model documentation. Is the report clearly written? Is it complete? Does it follow a logical structure and layout? Is it useful? If not, the reviewer shall provide an alternate outline and/or approach for adequately and clearly documenting this risk assessment.

As noted above, the model has essentially no documentation. The report explains the results from using the model, but is NOT a substitute for model documentation.

Response 75

Model documentation appears in Appendix C.

Comment 76

The report itself is generally clearly written, and I could follow almost all the logic and flow of ideas (see exceptions in page by page comments below). The document is still quite rough around the edges, and still contains quite a few "loose ends" like references to be added, etc. The report is largely complete, except as noted below. I found the structure and layout to be very clear. The report itself is very useful, and very clear.

Response 76

No response necessary.

Comment 77

g. Evaluate the approach taken to estimate illnesses due to consumption of HPAI. Does the data derived from the animal model provide a sufficient surrogate upon which to estimate human illnesses? Are there additional methods to better utilize these or other data? If so, what additional approach should be taken?

Given the extreme lack of data on the ability of HPAI to cause human illness, the approach taken to estimate illnesses due to consumption of HPAI is a reasonable one. Allowing the user to vary the r-parameter of the dose response model, provides a reasonable approach to look at different possibilities.

It might be argued that use of a different (non-exponential) DR model like Beta-Poisson should have been evaluated. Would it have been possible to refit the Schijven et al data to other models? Perhaps the authors should address this question.

In the end, given the limited data available, the data derived from the animal model does provide a sufficient surrogate upon which to estimate human illnesses

Response 77

We do not currently have the raw mouse data used to develop the surrogate HPAI dose-response and it is our belief that neither did Schijven et al. The MID50 reported by Nguyen et al., 2005 for a particular strain was simply used to solve for *r*. See Hazard Characterization, Section 5, for additional detail. Schijven et al. appear to have chosen the exponential because of its simplicity. In addition, the exponential is useful as it is biologically plausible, adequately fits the available data, and contains only one parameter.

To better address the uncertainty associated with using a mouse intranasal study to estimate this does-response, additional data were identified and used to develop an alternative dose-response. See section 6.3.5.1.

Comment 78

Detailed, page by page comments:

Cover page: Cover graphic obscures text at top of page.

Response 78

This has been fixed.

Comment 79

Page 11: It is microbiologically incorrect to speak of "elimination" of the virus. The sentence could be fixed by re-writing as: "… 165°F is predicted to result in negligible risk to public health." Another option would be to strike the entire bullet point, as sufficient details are provided in the bullet point below.

Response 79

The sentence has been changed to the first option suggested by the reviewer.

Comment 80

Page 11: The statement that "99.5% of eggs can be removed from commerce given a 3 day recall" seems very optimistic.

Response 80

No response necessary.

Comment 81

Page 11: "recommendations for egg products processing are sufficient to eliminate HPAI", same comment as above regarding the word "eliminate". Sentence could be changed to "recommendations for egg products processing are sufficient to insure negligible risk to public health".

Response 81

The work “eliminate” has been changed to “inactivate”.

Comment 82

Page 11: Grammar error “dried egg whites processing”, this should be singular: “dried egg white processing” as “white” is an adjective that modifies the noun “processing”.

Response 82

The text has been changed.

Comment 83

Page 12: Extra blank line after “needs are deemed most important following a sensitivity analysis”.

Response 83

Extra line removed.

Comment 84

Page 12: “relationship between the dose at consumption of HPAI-contaminated poultry and eggs”, the “and” should be “or”.

Response 84

The text has been changed.

Comment 85

Page 12: “window that could range…” should be “window OF TIME that could range…”

Response 85

The text has been changed.

Comment 86

Page 12: “eggs posed a negligible risk…” should be “eggs POSE a negligible risk…”

Response 86

The text has been changed.

Comment 87

Page 13: The sentence "In addition, effectively recalling shell eggs several production day backs will substantially reduce risk to consumers by eggs" is awkward and unclear. The phrase "production day backs" should be eliminated. Also, the risk is not from eggs, but rather HPAI-contaminated eggs.

Response 87

The text has been changed to: "In addition, effectively recalling shell eggs will substantially reduce the risk to consumers from HPAI-contaminated eggs."

Comment 88

Page 14: Extra blank line between 1.d. and 2.

Response 88

The text has been changed.

Comment 89

Page 15: Grammar error "This analysis is limited to strains of HPAI currently causing domestic poultry outbreaks in Southeast Asia and occasionally result in human morbidity and mortality". Suggest change to "This analysis is limited to strains of HPAI currently causing domestic poultry outbreaks in Southeast Asia and WHICH occasionally result in human morbidity and mortality.

Response 89

The text has been changed.

Comment 90

Page 15: The sentence "This risk assessment provides a comprehensive data-driven, systems analysis approach to collate available data, incorporate them into a mathematical

model, and provide risk managers a decision-support tool to evaluate the effectiveness of current and future interventions in reducing foodborne illness from HPAI in the U.S." is awkward

Response 90

The sentence has been removed.

Comment 91

Page 15: "Of most recent identification" is awkward and implies other subtypes. The sentence would be better if this phrase was dropped.

Response 91

Other subtypes do exist. For example, H9 appears to be zoonotic. The phrase has not been removed.

Comment 92

Page 16: "The risk assessment evaluates the public health risk associated with changes in the prevalence or level of HPAI in contaminated poultry products, shell eggs, and egg products. It will also examine…" two different tenses here. Pick one tense and stick to it.

Response 92

The sentence has been changed to: "It also examines the impact of changes in in-shell pasteurization, consumer cooking, and consumer handling."

Comment 93

Page 19: "LPAI viruses are generally not a public health concern and has…". The word "has" should be "have".

Response 93

The text has been changed.

Comment 94

Page 19: Footnote text needs to be added.

Response 94

The following text has been added: "Human infection with LPAI has been observed in the U.S. (2 cases of H7N2), China (7 cases of H9N2), and the U.K. (1 case of H7N7) (Swayne, 2006b)."

Comment 95

Page 22: "During bird-to-bird transmission within a poultry flock, airborne secretions of the virus constitute the major route of transmission". Can a reference be provided for this statement?

Response 95

The following reference has been added: Swayne and Halvorson, 2003

Comment 96

Page 22: Table 8 is cited here, but tables should be numbered in citation order. Either renumber the table or don't cite.

Response 96

"Table 8" has been removed.

Comment 97

Page 22: Why is a date given for the Swayne personal communication (8/15/2006), but not for other personal communications on the next page?

Response 97

Date has been removed.

Comment 98

Page 23: Nondetectable is misspelled: nondeteable.

Response 98

Misspelling has been fixed.

Comment 99

Page 29: Better define "effective contact rate". Is the numerator here birds contacted, i.e. 8 chickens /6 hours, 2 laying hen/6 hours, etc.

Response 99

Effective contact rate is defined in section 4.4.3.4. The text is made more clear by the following addition: 8 birds / 6 hrs – chickens and turkeys; 2 birds / 6 hrs – laying hens.

Comment 100

Page 29: Table 4 is cited here. Tables should be numbered in citation order.

Response 100

Table 4 is cited at this location because the data cannot fit into Table 2. The text remains the same.

Comment 101

Page 29: large discrepancy between 40.7 and 28.10 pound figures for turkey weight should be explained. It does become clear later in the document, but the text here is confusing.

Response 101

The text was incorrect to indicate that 28 lbs was the average weight for a turkey reared 20 weeks. 40.7 lbs is the appropriate weight for a turkey reared for 20 weeks.

Comment 102

Page 29: Source for egg weight needed.

Response 102

SERA, 2005 has been added to Table 2.

Comment 103

Page 30: Text says "Industry surveys (more detail)". Will more details be added?

Response 103

The variables that were referred to in the text were not used in the actual model. The text was removed.

Comment 104

Page 31: Figure 4 is cited. Figures should be numbered in citation order.

Response 104

See Response 100.

Comment 105

Page 31: "ARS unpublished avian influenza lethality study FDA analysis of ARS study - See Table" Which table?

Response 105

Text has been removed and reference added to substitute for "Table".

Comment 106

Page 31: "No data were identified to estimate the portion of cross contaminating virus consumed". It could be assumed that the virus would cross contaminate like bacteria. See Chen et al. 2001. Quantification and variability analysis of bacterial cross-contamination rates in the kitchen. Journal of Food Protection. 64(1):72-80. for example.

Response 106

The majority of bacterial contamination of poultry meat is surface contamination. Bacteria can be found adhering to the surface as well as within skin follicles. Viral contamination will likely also be found on the surface; however, the majority is in the interior of cells throughout the muscle. Therefore, it is difficult to estimate how representative bacterial cross-contamination will be compared with viral cross-contamination. Therefore, we have not chosen to use bacterial transfer rates as a surrogate for viral transfer rates (Chen Y, Jackson KM, Chea FP, Schaffner DW. Quantification and variability analysis of bacterial cross-contamination rates in common food service tasks. J Food Prot. 2001 Jan;64(1):72-80). For this risk assessment, we simply allow the user to input any value from 0 to 100% of the total EID50s associated with an HPAI-contaminated serving to be cross-contaminated and then ask the user to input how much will be consumed without cooking. This allows the user to explore the impact of cross-contamination on the model.

Some data were identified using virus cross-contamination experiments to estimate the proportion that could be cross-contaminated (Bidawid S, Malik N, Adegbunrin O, Sattar SA, Farber JM. Norovirus cross-contamination during food handling and interruption of virus transfer by hand antisepsis: experiments with feline calicivirus as a surrogate. J Food Prot. 2004 Jan;67(1):103-9.) Unfortunately, virus was inoculated directly onto the surface of ham, not giving a realistic characterization of the level of virus in the purge or on what would be expected on the surface of HPAI-contaminated poultry muscle. The authors of the study tested transfer of feline calicivirus from contaminated hands to ham and contaminated ham to hand. On average, 46% and 6% of the inoculum was found to be transferred, respectively. Given that ham to hands is a more realistic cross-contamination exposure pathway (the first step in cross-contamination is likely to be contaminated chicken transferred to hands and other surfaces), we can use 6% in the model to estimate the effect of cross-contamination. Using this value and then assuming all virus will be consumed (a conservative assumption), the model estimates an additional 0.2 expected illnesses.

The following text was added: “Additional data were identified using calicivirus cross-contamination experiments to estimate the proportion that could be cross-contaminated (Bidawid et al., 2004; D’Souza et al., 2006.) Unfortunately, Bidawid et al inoculated virus directly onto the surface of ham for testing of transfer to hands, not giving a realistic characterization of the level of virus in the purge or on what would be expected on the surface of HPAI-contaminated poultry muscle. D’Souza et al employed similar methodology when testing transfer from stainless steel to wet

lettuce. These studies found cross-contamination, on average, of 6.0 and 6.45%, respectively, of the virus being transferred."

Comment 107

Page 32: Poultry model: Some mention of the modeling software or modeling environment should be made here.

Response 107

This was overlooked. To indicate modeling platform, the following text was added to Appendix A: "The model is written in Microsoft Excel 2003 and has been tested in Microsoft Excel 2007 with Windows XP and Vista. Visual Basic for Applications is used to perform the combinatorial evaluations for different scenarios."

Comment 108

Page 34: Figure 2 would benefit from having an inset which zooms in on the time around 56 days and following where the mortality threshold is approached. The inset should focus on 0% to 2% mortality.

Response 108

The reviewer's response is appreciated; however, the figure is followed by a lengthy description in the figure label: "A chicken flock reared for 56 days (8 weeks) could be infected with HPAI within the last days before they reach market weight and are sent to slaughter (at 56 days). In this example, the flock is infected at 53 days. The progression of the disease shows that by the time the flock reaches 56 days, though many birds are infected with HPAI, few have died given that it take 36-42 hours for infected birds to succumb to HPAI. This flock would therefore be sent to slaughter without discovery of HPAI. In the shaded gray section is the progression of the disease had the birds stayed longer on the farm." A insert has not been added.

Comment 109

page 34; "100% detection ." delete space before period.

Response 109

The text has been changed.

Comment 110

Page 34: “pathonumoic”, did you mean: pathonomic?

Response 110

The text has been changed to “pathognomonic”.

Comment 111

Page 34: “a subjective” close up space.

Response 111

The text has been changed.

Comment 112

Page 36: If “flock size” refers to the number of birds in one house, shouldn’t this be more properly called “house size”?

Response 112

Depending on the size of the house, a single house can represent a single flock and vice versa. Text has not been changed.

Comment 113

Page 36: What does CGH stand for? Ah! Perhaps Cornish Game Hen? … still it should be spelled out.

Response 113

The text has been changed.

Comment 114

Page 37: Explain that 8 birds/6 hr is based on 32 birds/24hr divided by 6. What would be the effect of modeling a smaller amount of time, like 4 birds/3 hr?

Response 114

The sentence has been changed to: "Because bird mortality and prevalence of HPAI in poultry data is given every 6 hours (Table 4), for the baseline scenario, an effective contact rate of 8 birds every 6 hours is assumed for both chicken and turkeys."

The model cannot evaluate the effect of a shorter time frame given that we are limited by the data.

Comment 115

Page 39: "40% of infected bird" bird should be birds.

Response 115

The text has been changed.

Comment 116

Page 39: "of grams infected poultry" should be "of grams OF infected poultry".

Response 116

The text has been changed.

Comment 117

Page 40: "1.7 log10 HPAI EID50 present at 8 hrs in brain while 7.5 log10 at 48 hrs". Is the 48 hr data in brain as well?

Response 117

Yes. The text has been changed to: "1.7 $\log_{10}$ HPAI EID_{50} present at 8 hrs in brain while 7.5 $\log_{10}$ in brain at 48 hrs; D. Swayne, 2006 personal communication."

Comment 118

Page 41: "Working from this maximum level, the level of HPAI was decreased by a factor of 5 every six hours" What is this decrease assumption based on? Published data? Opinion? Guess?

Response 118

The following text has been added to the report: "The rate of decrease was chosen given that HPAI virus will likely replicate exponentially given optimal growth conditions. However, few data were identified to estimate the magnitude of this decrease." In addition, the levels prior to peak infection were re-evaluated: "Therefore, the 21 H5N1 level estimates for chicken breast and thigh meat were averaged to determine the expected value for the level of HPAI in chicken meat (Table 5). $10^{7.7}$ EID_{50}/g HPAI H5N1 was used as an upper bound to indicate the level of HPAI in poultry meat of dead birds at 43 hours. Das et al, 2006 observed HPAI-infected birds dead at the latest by 42 hours. Forty-three hours was the next appropriate 6-hour time interval and was therefore chosen to represent the maximum level of virus. Working from this maximum level, the level of HPAI was decreased exponentially every six hours until the 7-hour time interval was reached. (Figure 5). Das et al., 2006 indicate that HPAI could be detected at 6 hours post-infection by testing of embryonated eggs. The level of detection for this method was 1.9 EID_{50}/g HPAI and is used to estimate the level of HPAI in muscle of 7 to 12-hour old infected birds. Model options allow 10-fold increases or decreases to the level of HPAI in infected poultry meat to estimate the impact of this assumption (see Appendix B: Model Options). These data are assumed representative of turkeys."

Comment 119

Page 44: Comments should be removed from final document.

Response 119

Comments have been removed.

Comment 120

Page 45: Add references to final document.

Response 120

No response necessary.

Comment 121

Page 45: "The risk posed from egg type birds is in the eggs which could have been produced before the flock was diagnosed. Thus, the egg model starts at the point of diagnosis and looks back into the past to estimate the number of eggs that could have gone to processing prior to detection." The phrase "egg type birds" is jargon. The sentence should be re-written to read "In this case, the risk is posed by eggs produced by an HPAI-infected flock, where those eggs were laid before the flock was diagnosed". Also eliminate the phrase about "looking back into the past", so that the sentence reads "Thus, the egg model starts at the point of diagnosis and estimates the number of eggs that could have gone to processing prior to detection".

Response 121

The text has been changed.

Comment 122

Page 47: "Unlike the poultry model, "weeks in house" and bird type are not needed for the egg model." Explain why…

Response 122

The following text has been added: "For the egg model, the size of an egg is considered uniform (60 grams). However, for chickens and turkeys, the size of the bird increases as the bird is reared for longer periods of time. The more meat associated with a dressed carcass, the greater the potential exposure. "Weeks in house" and "bird type" are associated with changes in the magnitude of the exposure (bird size) and are therefore not needed for the egg model."

Comment 123

Page 50: The phrase "The model parameters that determine the amount of HPAI reaching consumers through shell eggs are" should end with a colon, since it precedes a list.

Response 123

The text has been changed.

Comment 124

Page 51: Add REF where indicated.

Response 124

The text has been changed.

Comment 125

Page 51: Although "Time for eggs to reach consumers" is discussed here, what assumptions are made about survival or replication of the virus in eggs? This is addresses much later, but it would also be appropriate to comment here.

Response 125

Factors that could have an impact on survival of HPAI in food are discussed in the hazard identification, Section 3.7: Factors Affecting HPAI Survival. In addition, a new section has been added to address data availability supporting this assumption: Section 4.6.7: HPAI survival during storage. Inactivation during storage of HPAI-contaminated poultry and eggs was not modeled as data to estimate a daily inactivation rate under various storage conditions were not identified. Therefore, it was assumed that the level of HPAI does not decrease during storage as product should be maintained at about 4°C. Using other viruses, the following data support this assumption: Pearson, 1944 conducted several experiment using influenza type A and showed that the virus suspended in alloantoic fluid "at 4-6 C retained its original titer" for at least 15 days. In addition, Lynt, 1966 found that poliovirus and coxsackievirus stability was dependent on the food matrix in which it was tested— surviving well in potato salad for up to a month but not pizza or shrimp. A more recent study using feline calicivirus as a surrogate for norovirus inactivation on the surface of ham found about a 1 log10 decline in virus titer over 1 week at 4°C (Mattison et al., 2007). However, these studies tested the effect of drying and the authors attribute the relative stability of virus on ham due to seepage "through the surface of the ham to an inner matrix, thereby being protected against dryness." Given that most HPAI will be internal, this study is not likely representative. A review paper indicated Sobsey et al., 1986 stated "HAV [hepatitis A virus] did not decline over 8 weeks in groundwater or soil samples and none of the three viruses [HAV, poliovirus, echovirus] declined in the effluent samples at 5°C" (John and Rose, 2005). Alternatively, virus titers have been observed to decline in ground water and other matrices over time. This is largely dependent on

temperature where refrigeration temperatures reduce or inhibit inactivation (John and Rose, 2005). Collation of data from six virus types suggests that the mean rate of decline ranges from 0.03 to 0.2 log10 per day (data from experiments using 3-30 °C)."

Comment 126

Page 53: Remove comment.

Response 126

Comment has been removed.

Comment 127

Page 54: "comleted" is misspelled.

Response 127

Misspelling has been fixed.

Comment 128

Page 55: Clarify that the "7.0 $\log_{10}$ heat step" mentioned here is for *Salmonella*.

Response 128

Sentence has been changed to: "ARS researchers demonstrated that chicken muscle contaminated with high titers of HPAI virus ($10^{8.5}$ EID_{50}/g) were eliminated following a 7.0 $\log_{10}$ heat step required for *Salmonella* (Thomas and Swayne, 2006)."

Comment 129

Page 55: In addition to "Ready-to-Eat and Partially Cooked Poultry" the authors may wish to specifically exclude from the risk assessment poultry that <u>appears</u> to be ready-to-eat, but in fact is uncooked and breaded. This class of foods has caused some outbreaks, and a recent NACMCF document (Consumer Guidelines for the Safe Cooking of Poultry Products) touches on the subject.

Response 129

The reviewer is correct that such products have resulted in bacterial outbreaks probably due to undercooking of raw poultry that appeared cooked. The model in fact incorporates such products by allowing 29% of the raw poultry serving from an infected flock to be cooked at 135°C or less. The reason for specifically not including the impact of RTE or PCF is that the model does not mechanistically model the impact of a cook or partially cook step at a poultry processing plant.

Comment 130

Page 57: Add REF noted here.

Response 130

Reference has been removed.

Comment 131

Page 61: "suprisingly" is misspelled.

Response 131

This word is part of a quote. The misspelling has not been changed.

Comment 132

Page 61: Table on this page has no number.

Response 132

Table number has been added. Subsequent tables have been renumbered.

Comment 133

Page 62: "Peter, what IS the answer?"

Response 133

Comment has been removed.

Comment 134

Page 62: The "recent review" cited here should be formatted as a normal reference.

Response 134

Text has been removed.

Comment 135

Page 62: Table on this page is also missing a number.

Response 135

See Response 132.

Comment 136

Page 64: Why was a 6 hour time interval chosen? Why not 4, 8 or some other value?

Response 136

A 6-hour time interval was chosen given the paucity of available time course data. The ARS study, Das et al., 2006, observed and sampled chickens every 6-hours following experimental infection with HPAI. Data are not available for 4 or 8 hours (or multiple of this numbers). The following text was added to the report: "The time interval of 6-hours was used given the data of Das et al., 2006 (Table 4). Data were not identified for other time intervals."

Comment 137

Page 65: Remove comment.

Response 137

Comment was removed.

Comment 138

Page 65: The table indicates 0.4 dead birds. What is a bird that is 40% dead? Is it like Schrodinger's cat? ☺ Likewise, what is 0.10 or 0.45 of an illness?

Response 138

The reviewer's sense of humor is appreciated. We agree that this is odd to conceptualize; however, this is simply a product of the probabilistic component of the risk model. The transmission model predicts the number HPAI infected birds over time. Given that there is a factional probability that birds will be in different states over time, the model generates fractions for the number of dead birds. In addition, the model predicts the probability of illnesses using the dose-response function. This in turn will produce fractional illnesses.

Comment 139

Page 65-66: The statement is made that "Therefore, the model predicts that a chicken or turkey flock infected with HPAI is only a risk if the birds are infected when they are close to market weight." It is not so much the model that predicts this, as the assumption that flocks with 2% or greater mortality are not sent to slaughter. I don't disagree with the statement, only that it doesn't take a model to make this assertion.

Response 139

We respectfully disagree with the reviewer. The statement "the model predicts that a chicken or turkey flock infected with HPAI is only a risk if the birds are infected when they are close to market weight" would be accurate even if the model assumed that a flock with ≥0.1% or ≥99% mortality are not sent to slaughter. The model predicts that 2.5 to 6.3 days, respectively, would constitute the time range in which if a flock was infected, it would be sent to slaughter. This window of time is due to how the model predicts the number of birds that are dead over time (the transmission model). If the model predicted a much slower spread of HPAI, such as an effective contact rate of 1 (only one bird infected every six hours), then the model predicts the range increase from 6.3 to > 14 days in which a flock could be sent to slaughter.

Comment 140

Page 66: "flock will be determined as HPAI" should be "flock will be determined as HPAI-positive."

Response 140

Text has been added.

Comment 141

Page 66: Although footnote 22 points out the limitations of the preceding statement, I think the statement itself should be removed. It's a bit silly to claim that a flock could be detected one 1 hour after infection, since this means a single bird is infected. The odds of that single bird being included in the sample of birds from a flock of 9,000 or 20,000 are very low. I suggest keeping the first sentence of paragraph, striking the rest, and adding the text of the footnote into the paragraph directly.

Response 141

To address the reviewer's comment, a more rigourous analysis has been completed and the footnote removed: "Table 18 demonstrates testing programs where an infected chicken flock is sampled for HPAI before it goes to slaughter. These scenarios assumes that 65 birds die per day due to other causes besides HPAI (~0.3% daily mortality (Tabler et al., 2004)) for a 20,000 birds chicken flock within the last week prior to slaughter and a 0.882 probability of detecting 1 positive sample using the RRT-PCR (Spackman et al., 2003). Dead chickens tested immediately before a flock is supposed to be sent to slaughter can reduce the number of HPAI-positive flocks entering slaughter and the relative risk associated with the HPAI-infected index flock. The relative risk reduction levels off at ~97% because not all 6-hour time intervals in which a flock could be infected with HPAI can be detected as HPAI-positive by testing. That is, flocks infect within 38 hours of being sent to slaughter will not be detected given that there are no dead birds from HPAI."

Table 18. Effect of testing flock for HPAI prior to slaughter.

# DEAD BIRDS TESTED PRIOR TO SLAUGHTER	RELATIVE RISK REDUCTION (%)
5	91
7	94
9	96
11	97
13	97

Comment 142

Page 66: Table 17: It's not clear what assumptions are operating in Table 17. If the flock is infected close to slaughter, and the number of ill or dead birds is low, it's unrealistic to assume that (even with a test that detects the virus with 100% accuracy) a positive bird will be selected for testing. In other words, the key factor is the odds of selecting a bird which contains the virus. If testing were used, how many birds would be selected for testing?

Response 142

See Response 141.

Comment 143

Page 67: Figure legend reads "Flocks infected greater than 73 hours are detected…". This should be changed to "Flocks infected more than 73 hours prior to slaughter are detected…"

Response 143

Text has been changed.

Comment 144

Page 68: for the sentence "FSIS recommended consumer cooking of poultry to 165°F is predicted to result in elimination of the virus and negligible risk to public health" see comment above for the same sentence in the executive summary.

Response 144

Sentence has been changed to "FSIS recommended consumer cooking of poultry to 165°F is predicted to result in negligible risk to public health."

Comment 145

Page 68: As above, in Table 18, what is a fractional illness?

Response 145

See Response 138.

Comment 146

Page 69: "Using scenario analysis, the model can estimate what if more consumers cook to the FSIS recommended poultry temperature than is currently assumed by the baseline scenario?" Awkward sentence.

Response 146

Sentence has been changed to "Using scenario analysis, the model estimates what if more consumers cook to the FSIS recommended poultry temperature than is currently assumed by the baseline scenario."

Comment 147

Page 69: "By considering different cooking temperatures, the model can show if such an outreach campaign would be effective in lowering potential human illnesses and if so, to what degree" It is important to point out that the model can only show the effect of changes to consumer behavior, NOT the effectiveness of the outreach campaign. To understand the impact of the outreach campaign, the ability of the campaign to change behavior would first need to determined (or assumed). Changing consumer behavior is notoriously difficult.

Response 147

To address this issue, the following text has been added "The model does not assess the feasibility of this mitigation strategy, but rather by showing the degree of effectiveness, demonstrates the potential usefulness, or lack thereof, of such an approach."

Comment 148

Page 69: It is not clear how the data in Table 20 relate to the data in Table 6. For example, 17.4 + 11.2 = 28.6, and with 10 degrees added to the cooking temperature, the 11.2 percent at 145 are now cooking to 155, but where does the value of 8.6% arise from? Also, since Figure 4 shows a small fraction of chicken that is cooked to 109 ºF, even if the cooking temperature is raised to 109+30 = 139, this would result in some virus survival.

Response 148

The value of 8.6% arises from those consumers that were observed cooking poultry so low that even an increase in 20 ^{o}F is still below 155 ^{o}F

(Note, 155 ^{o}F represents the range 150-159 ^{o}F). A footnote has been added: "8.6% is the percent of individuals observed to cook poultry at <100-129 ^{o}F. Therefore an increase of 20 ^{o}F would still result in cook of 149 ^{o}F or less". The original text has also been modified: "The model estimates the effect of a cooking outreach campaign by simulating what would happened if the assumed 28.6% of consumers that cook poultry less than 155 ^{o}F[2] increased their current peak cooking temperature by 10 ^{o}F (28.6 - 11.2 = 17.4%) or 20 ^{o}F (17.4 - 8.8 = 8.6%)."

Comment 149

Page 70: "however it is reasonable to estimate that liquid covering a surface that would interface with a salad components, for example, would be no greater than 1 mL assuming no pooling." Awkward ("interface") and grammatically incorrect "a salad components". Also "pooling" needs to be explained.

Response 149

This section has been modified to more accurately represent the model. Therefore, the sentence in question has been removed.

Comment 150

Page 70: According to Figure 8, the statement "If the level of HPAI in purge is greater, cross-contamination contributes more to the total number of predicted human illnesses" is only true when the proportion of cross contaminated virus consumed is 0.01 or less.

Response 150

The following footnote has been added: "As the level of HPAI in the purge increases, but the proportion that is cross-contaminated decreases, less illnesses are predicted. This is because the model subtracts the cross-contaminated virus from the poultry serving."

Comment 151

Page 72: Since this is a section on eggs, the statement "Unlike eggs, poultry production is based on an "all-in all-out" model." Should be reversed to read: "Unlike poultry, egg production is NOT based on an "all-in all-out" model." And change the sentence "Therefore, one can estimate the probability the entire flock will go to slaughter" to read

[2] Recall that 155 ^{o}F represents a range of temperature between 150-159 ^{o}F (Table 6).

"So one can not estimate the probability that an entire flock's worth of eggs will be processed" or some equivalent statement.

Response 151

The text has been changed for the first sentence and not changed for the second sentence.

Comment 152

Page 74: As above, some discussion of what a fractional illness means is needed. Also some explanation of what type of food is a mixture. Also, the values (excluding mixtures) sums to 100.3%.

Response 152

Please see Response 138 for explanation of fractional illnesses. Mixture is defined as those eggs that are used as ingredients, *e.g.*, during baking. The sum of 100.3% is due to the issue of rounding.

Comment 153

Page 75: What assumptions are made about recall effectiveness? Are the recalls assumed to be 100% effective? If so, what data support this? This is discussed on the next page, but the point needs to be made up front.

Response 153

When estimating the effectiveness of a recall, the model assumes that all contaminated eggs can be recalled, regardless of when the egg was produced. In reality, an actual recall will not likely be able to recall all eggs produced by the HPAI-infected flock. Effectiveness of a recall will depend on many factors including 1) time of eggs to reach market shelf, and 2) rate or response by industry, retail, and consumers to the recall.

Data were not identified to estimate the effectiveness of a recall. For example, *when* an HPAI-positive egg is produced will affect the probability that the egg can actually be recalled. HPAI-positive eggs recently laid by a discovered layer flock and still on the farm will have a high probability of being successfully recalled, where HPAI-positive eggs produced 4 or 5 day ago, may have a low probability of recall (these eggs may be somewhere in the distribution chain and difficult to track). Data to inform these probabilities is not likely to change the outcome of the scenario analysis because most HPAI-positive are predicted to be laid very near when the flock is identified as HPAI-positive. These eggs will easily be

recalled given that it requires about 6 days for eggs to reach the market. HPAI-positive eggs produced earlier in the infection may not be recalled, but these constitute a small fraction of the total HAPI-positive eggs produced by the flock.

Comment 154

Page 76: What does "disappearance" mean in this context? Disappearance is sometimes a surrogate for purchase, but since purchase is listed in the same sentence, its meaning is unclear.

Response 154

Disappearance refers to the food prepared but not consumed, such as leftovers that are thrown away. This was removed from the report.

Comment 155

Page 78: "Figure, 12" delete comma.

Response 155

Text has been removed.

Comment 156

Page 78: "exponential decay relationship" is modelers jargon.

Response 156

The text accurately describes the relationship between time and HPAI-contaminated egg production and has not been changed.

Comment 157

Page 81: It is not clear how the "2.4 fold increase" value is derived from Table 27.

Response 157

The mean values for the table to which the increase refers has been added. It should be clear from the new table where this is derived.

Number of hours that flock is infected before slaughter	Number of birds initially infected			
	1	10	100	1,000
	Predicted human illnesses			
1	0	1	10	98
7	0	4	44	437
13	1	13	126	1,219
19	3	30	299	2,634
25	7	70	674	5,080
31	17	173	1,561	
37	44	432	3,294	
43	111	1,038	3,869	
49	272	2,367		
55	660	4,296		
61	1,551	2,261		
67	3,401			
73	4,203			
Mean	790	971	1235	1894

Comment 158

Page 81: It seems that one reason for the difference caused by number of bird initially infected is the rate of increase of human illnesses as a function of "number of hours that flock is infected before slaughter". The human cases are linked to similar rapid increases in bird infection rates. It seems to me that this shows the importance of the choice of a 6 hour window (see comment above on page 64). A longer window would allow more infected birds through before the 2% cap was exceeded, while a shorter window would allow less. The authors may wish to explore window size as a variable within the model. If not, at least the potential importance of this choice should be discussed.

Response 158

The reviewer makes an interesting comment regarding the impact of a shorter or longer time interval. The 6-hour time interval is a fact of the data rather than a choice. The reviewer is correct that a smaller window would have the effect of the model updating the percent mortality more often; while a longer time window would have the opposite effect. This would have an effect on the number of HPAI-positive birds allowed to go to slaughter. Given that the data dictate the time interval chosen, we have not explored different time intervals. Text has been added to the main report to clarify the choice of the 6-hour time interval: "The time interval of 6 hours was used given the data of Das et al., 2006 (Table 4). Data were not identified for other time intervals. Shorter or longer time intervals would likely have an impact on the number of HPAI-positive birds sent to slaughter."

Comment 159

Page 81: Clarify is the discussion of the "egg-type flock" that the data are "not shown".

Response 159

Text has been changed to "egg-producing flock" and "data not shown" has been added.

Comment 160

Page 82: "the shape of the curves vary" grammar error.

Response 160

Text has been changed to "shape of the curves varies".

Comment 161

Page 82: "one must recall" best not to use the word "recall" since it has other meanings in the document. Use "note" or "remember" instead.

Response 161

Text has been replaced with "remember".

Comment 162

Page 82: Table 28 duplicates the data shown in Figure 14, and adds a column for "Maximum at risk window (hours)". Consider deleting the table, or at least the repeated data.

Response 162

The table has usefulness though the reviewer is correct that it is duplicates the figure.

Comment 163

Page 83: "The model then assumes an exponential decline, decreasing the level of HPAI/g by a factor of 5 every 6 hours prior to peak infection" The phrasing here is odd, and seems to imply that time is running backwards, i.e. the levels are declining prior to peak infection. This may be the way the calculations are done, but the language could be clarified: "The model assumes the levels of HPAI/g increase by a factor of 5 every 6 hours up to peak infection levels of $10^{7.3}$ EID_{50}/g".

Response 163

The text has been changed to the reviewer's suggestion.

Comment 164

Page 84: Clarify that the x axis is average EID50/g poultry meat AT PEAK INFECTION. Also the figure should indicate where the baseline value is on the plot. Also clarify if illnesses are from chicken, turkey or egg scenario.

Response 164

The reviewer is correct that the labeling of the graph was confusing. When the peak level of HPAI is altered in the model options, each HPAI level at the preceding 6-hour intervals is also changes by a factor of 10. The x-axis is represented by the peak level, but actually represents a distribution of levels that is a function of length of bird infection.

To address the reviewer's comment, the figure legend now clarifies that the data presented in this figure is for chicken and turkey.

Comment 165

Page 84: "Because the percent mortality inspectors would condemn a flock is unknown" grammar error. "Because the percent mortality value that inspectors would use to condemn a flock is unknown" is better.

Response 165

The text has been changed.

Comment 166

Page 87: Include baseline value indicator on Figure 18.

Response 166

The following text has been added to the figure legend: "A baseline value of 6 days is used in the model."

Comment 167

Page 87: "However, similar data needs listed in previous risk assessment (Table 1) have been referenced were appropriate." Grammar and spelling errors: "However, similar data needs listed in previous risk assessments (Table 1) have been referenced where appropriate."

Response 167

Text has been removed.

Comment 168

Page 87: "Further research needs will be identified during model development" Isn't the model already developed?

Response 168

Text has been removed.

Comment 169

Page 87: "replace the data"… I suggest "update" rather than replace.

Response 169

The text has been changed to the reviewer's suggestion.

Comment 170

Page 115: Egg model options header appears to be mis-numbered.

Response 170

Header has been renumbered.

Comment 171

Page 117: section 9.2 doesn't seem to exist.

Response 171

Thank you, this header has been removed.

8 REVIEWER NUMBER 5

Comment 172

Specific responses to the questions below.

h. Is the overall approach for modeling the risk of HPAI from consumption of HPAI-contaminated poultry, shell eggs, and egg products, as described in the report, fundamentally sound? Specifically, is the use of a combination of scenarios, given the availability of data, as opposed to a probabilistic approach, appropriate? Does the combinatorial approach adequately answer the risk management questions and would these models be useful in guiding and prioritizing emergency and preventive measures, and guiding risk communication messages should HPAI be detected in the U.S.? If not, what problems exist and how should they be addressed

The risk management questions are:

1. What is the risk of human illness from consumption of HPAI-infected poultry meat, shell eggs, and egg products?

2. What is the effectiveness of interventions to reduce human exposure and illness from the introduction of HPAI into commerce from shell eggs? The following scenario analyses were also be addressed:

    a. Evaluate the reduction in human exposure to HPAI from infected shell eggs assuming the infected flock is identified and closed following various days after infection.

    b. Evaluate the reduction in human exposure to HPAI from contaminated shell eggs following market withdrawals/recalls of eggs laid various hours (*e.g.* 12, 24, 48, 72, and 96 hours) before the house was identified as infected and closed.

Question No. 1 is very reasonable and the assessment indicated there is a risk from consumption of both poultry and eggs even if there is considerable uncertainty. Interventions are considered in Question No. 2 for shell eggs but not for poultry. Mitigations are briefly mentioned under 6.1.5. Perhaps this could be included as a goal and the three possible mitigations (earlier detection [also applies to shell eggs], chemical decontamination, and cooking) given more discussion. For the eggs, mitigations are mainly early detection and pasteurization.

Response 172

Effect of testing flock for HPAI prior to slaughter mitigation strategy is given in Section 6.1.2.1. The reviewer is correct that more discussion in this section is needed. See Response 141.

Comment 173

I am not familiar with the combinatorial approach and it will be new to many readers and should have a more detailed explanation. It is briefly described on page 26 but this is not enough. Are there any previous uses of it especially where described in published papers? However, I understand that there is not enough data for probabilistic risk assessment.

Response 173

Additional text has been added to clarify the combinatorial approach and impact: "Conventionally, the combinatorial approach to uncertainty analysis is a method where each factor is assigned a limited set of discrete values, e.g., low, nominal, and high values (Morgan and Henrion, 1990). Then, while keeping the other inputs at their nominal (e.g., central or expected value) values, we calculate the effect on the output of varying each input from its low to high values. These effects, often called "swing weights," are used to identify important model inputs. The combinatorial approach is also useful for exploratory analysis to identify the combinations of inputs values (scenarios) that lead to the worst (or best) predicted outcomes. Stated differently, this approach allows users to evaluate the effect of each parameter and its accompanying uncertainty on the estimated number of human illnesses due to consumption of poultry or eggs from HPAI infected flocks."

Morgan and Henrion, 1990 discusses the combinatorial approach.

Comment 174

The baseline approach seems to indicate that a most likely value is selected, e.g., most likely proportion of birds dying after 36 hours is 0.4 but it could be 0.2 or 0.6. How does this differ from a triangular distribution? It seems that the combinatorial approach uses point estimates without a distribution. From what I gather the tails are not included because they are considered so rare (page 27).

Response 174

The combinatorial approach does, for the most part, use point estimates instead of distributions. However, if one wants to know the impact of a tail

of a distribution, one only needs to select an option or make a simple change to input options. The model is a scenario analysis and therefore distributions are not considered.

Comment 175

A subgoal could be to suggest areas for research or surveys to improve the data used and the sensitivity analysis. Research is briefly mentioned on section 7, page 88.
From the sensitivity analysis, risk communication strategies and preventative measures can be developed, e.g., flock observation when suppliers purchase potentially contaminated birds, or when there are reports of wild bird mortality in the area; thorough cooking (this is a standard risk communication message anyway to destroy pathogens like *Salmonella*).

Response 175

Risk communication strategies and preventative measures can be derived from this risk assessment; however, this risk assessment report is not the appropriate place to discuss or elaborate on specific messages.

Comment 176

i. Review the available data and derived variables in conjunction with the underlying assumptions used in this risk assessment.

    1) Have all key studies and data been identified? If not, the reviewer shall provide additional data sources and citations (where appropriate).

Data sources quoted and use (Table 2) are frequently industry sources, personal communications or unpublished data. However, if we are to wait for only published papers, this assessment may never be done and the risk from consumption possibly ignored. What this assessment does is to indicate that human infection from broilers, turkeys or shell eggs is possible and warning information for the public (and industry) can be generated ahead of an event created from the mitigation areas suggested. However, it appears that more research should be conducted now to generate the missing data since there is a potential for illness from AI-contaminated products.

Response 176

Data needs are given in Section 7. These data needs have been informed by a sensitivity analysis. In addition, research should only be conducted if managers' questions are not answered.

Comment 177

Table 2 is the closest the authors get to put all the assumptions and data points together but this is not complete. Other assumptions are given in the text. Could there be a large table with the data used, assumptions made and formula used, even if in an annex?

Response 177

Table 2 has been modified to include this.

Comment 178

The recent poultry outbreak in the UK is worth examining because there were delays in notification (possible traceability issues from imported birds and a large company trying to sort out the problem of dying birds without informing the government soon enough). Example below gives useful data.
Data on the Upper Holton, Suffolk, UK H5N1 turkey outbreak on January 27 2007 (http://www.oie.int/eng/info_ev/en_avianinfluenza.htm).

Affected animals

Species	Susceptible	Cases	Deaths	Destroyed	Slaughtered
Birds	159000	7000	2500	152000	0

Outbreak statistics

Species	Apparent morbidity rate	Apparent mortality rate	Apparent case fatality rate	Proportion susceptible removed*
Birds	4.40%	1.57%	35.71%	97.17%

- Removed from the susceptible population either through death, destruction or slaughter

Response 178

The risk assessment does not address effects of delays in notification and possible consequence of such delays. The model assumes that once a flock reaches a certain daily mortality, the flock will be held and not sent to slaughter.

The recent HPAI outbreak does provide information on the transmission of H5N1 within a commercial turkey farm. Mortality data from the U.K. turkey were obtained through a personal communication with (John Wilesmith, personal communication). The data are given in the table below and graphically represented in the first figure. These data were incorporated into the transmission model to compare the rate of mortality predicted by

the model and that reported during the recent outbreak (the second figure).

U.K. turkey outbreak data over time.

	27-Jan	28-Jan	29-Jan	30-Jan	31-Jan	1-Feb	2-Feb
No. Dead	6	7	8	13	156	860	1580
Rate of spread		1	1	5	143	704	720
% of flock	0.084%	0.098%	0.112%	0.183%	2.191%	12.080%	22.194%
Days post detection	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7

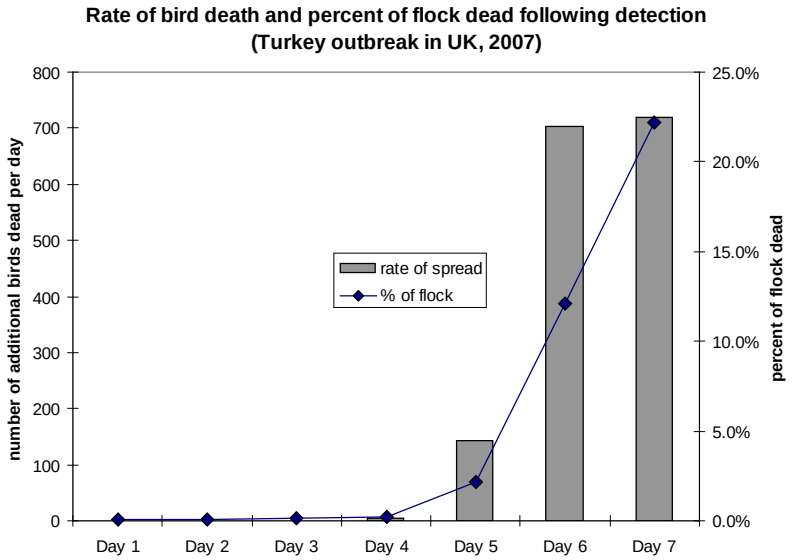


Figure. Graphical U.K. turkey outbreak data.

Given that it is unknown when the flock was actually infected, a direct comparison without uncertainty is not possible. However, if it is assumed that the first time point in which the model predicts mortality and the observed mortality are “lined up”, then the observed data suggest that H5N1 in this turkey flock is spreading at a lower rate than that currently being used by the baseline model. The data in the figure suggest that the rate of transmission and subsequent mortality can be quite variable.

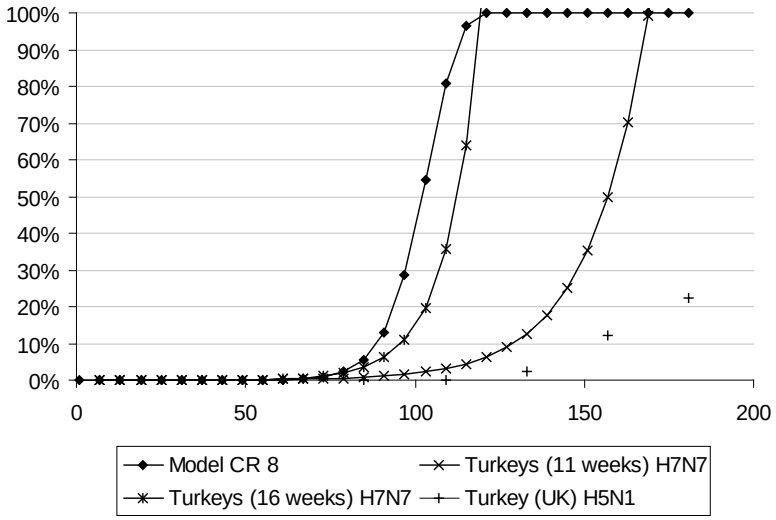


Figure. Model predictions based on a contact rate of 8 (assumed baseline for chickens and turkeys). Turkey mortality data for H7N7 infected flocks from the 2003 HPAI Netherlands outbreak (Elber et al., 2007) have been added for comparison. (Y-axis: daily flock mortality; X-axis: hours from initial infection)

Comment 179

Also, Strain H7N7 is quoted a few times relating to human illnesses and one death in the Netherlands. Yet, it is excluded from this assessment. Presumably, this is because it causes conjunctivitis through direct contact and not through consumption (but do we know this for sure?) and a brief explanation can be given for its exclusion.

Response 179

H7N7 is not excluded from the risk assessment. The risk assessment focuses on strains that are currently circulating in Asia, Africa, and the Middle East and that result in human infection and illnesses. Any strain that could result in human infection and illness can be addressed by this risk assessment; however, the data used in the risk model baseline are assumed to be representative of H5N1. For example, if one wanted to estimate the exposure and risk of illness from H7N7, one needs only populate the model with data specific to this strain. Does the strain spread as quickly as we expect of H5N1? Is the HPAI baseline level used representative of H7N7 and is the dose-response adequate. etc? In addition, the model does not address the impact of severity of illnesses. In other words, we do not estimate hospitalizations and deaths from infection with HPAI. This is important and allows the risk model to be used with any strain of HPAI.

The following language appears in the risk assessment: "The scope of this assessment is limited to where FSIS, FDA, and to a lesser extent, APHIS have direct statutory authority that could impact HPAI as a food safety concern. This analysis is limited to strains of HPAI currently causing poultry outbreaks in Asia, Africa, and the Middle East and which occasionally result in human morbidity and mortality. This analysis does not apply to HPAI strains that are occasionally detected in U.S. poultry flocks but are rarely associated with human infection."

Comment 180

There could be more background into cases of the illness in developing countries; no Chinese, Vietnamese or Thai studies (or any of the countries where illnesses and deaths have occurred) are quoted. According to page 9, the human death rate is >50%. There are probably some epidemiological data to see if any of the illnesses and deaths could be related to consumption of poultry or at least in contact with locally reared broiler-type carcasses or eggs (pages 25 and 57).

Response 180

To date, it is our understanding that there are very few epidemiological data that support the role of consumption as an exposure pathway for HPAI in humans. Several epidemiological studies have investigated this possibility and found that either a role for consumption could not be confirmed and/or consumption was not associated with risk of illness. The following text appears in the report: "Currently, there is no epidemiological evidence linking the consumption of raw or undercooked poultry, shell eggs, or egg products to human illness from AI. Only two cases suggested a possible link to the consumption of raw duck blood, though contact with live or dead HPAI-infected poultry cannot be epidemiologically excluded (EFSA, 2006)." An in-depth analysis of the available epidemiological data has been done (see Appendix D).

Comment 181

2) Have the data been correctly interpreted, analyzed, and used in the risk assessment? If not, the reviewer shall provide alternate interpretations, analysis, or suggested utilization of the data.

3) Please address the validity and appropriateness of all input data in the model.

For 2) and 3), I have no general comments on the correctness of the assessment or its validity. Specific comments are given on the text in the Annex, which relate to these points.

Response 181

No response necessary.

Comment 182

Some of the data inputs and assumptions are listed in Table 2. The data used are means mostly from industry representatives or unpublished data. The table is useful as it does summarize these inputs. However, I think it would be useful to the reader to also see the range of the data points, e.g., mean flock size is 20,000 but what is the smallest being considered and the largest known? Note on page 36 a range is given of 100-120,000 birds that "can be used as input to the model" (were they?). The larger the spread in these data points the more uncertainty there is, but for many of the data points the spread will be minimal such as production weeks. Eventually, these points could be used for triangular or other distributions. Are data points leaning towards conservatism or best guess?

Response 182

As the reviewer notes, the range is given in the text of the document. We have developed a user's manual for the models and input ranges are given there again. Again, the model is a scenario analysis with a series of "what if" scenarios. Therefore, a triangular distribution cannot be used in the model the same what as it would be implemented in a Monte Carlo analysis. However, the user could input a range of possible values. This would be similar to simulating a distribution. The data points are those model inputs that represent the baseline. They are a best guess.

Comment 183

j. Review the complexity of the model. Is the model too complex or not complex enough to adequately address the risk management questions? Is the model over or under parameterized? State whether the model adequately characterizes the uncertainty present and whether variability has been addressed sufficiently. In areas where the reviewer identifies limitations, weakness, or inadequacies, the review shall provide alternate data, data analysis, and/or modeling approaches.

The model is based on chicken (flock) mortality. Yet, distinctive symptoms occur before death even if only a short time before, which might at least be considered as a mitigation (more observance of a flock for potential illness, especially if there was a risk of AI in the

community). The UK data indicates the point where the flock was culled. Apparent morbidity in turkeys was greater than apparent mortality (4.4% vs.1.6%).

The model does account for much uncertainty which is inevitable in this kind of assessment.

Response 183

We chose to use flock mortality as in indicator of HPAI infection as this is a more objective measure. Measurement by flock morbidity is more subjective and would be dependent on the HPAI strain, bird type, time of year, ability of poultry managers to identify signs specific to HPAI infection, environmental conditions, etc (Elbers et al., 2003). If a strain is classified as HPAI, it is, by definition, a strain that kills ≥75% of infected chickens. Therefore, morbidity is a more reliable metric and will be more consistent between farms as well as within farms (Elbers et al., 2003).

More importantly, flock infection with HPAI does not present signs that are necessarily specific to HPAI (Elbers et al., 2003; Swayne and Halvorson, 2003). Following a study that evaluated the sensitivity and specificity of using various clinical signs for chicken, turkey and hen flocks infected with H7N7, Elbers et al concluded that "there is a solid basis for the choice of using increased mortality… as an early warning system for HPAI outbreak" and not the use of morbidity. In addition, Swayne and Halvorson observed "in most cases in chicken and turkeys the disease is fulminating, with some birds being found dead prior to the observance of any clinical signs."

Comment 184

k. Evaluate the risk assessment model source code and mathematics.

   1) Are the modeling techniques (model mathematics and equations) appropriate? If not, the reviewer shall provide alternate modeling techniques.

   2) Are the methodologies used in the risk assessment for estimating parameters from the data appropriate (*i.e.*, follow scientifically accepted methodologies)? If not, the reviewer shall provide an alternate approach.

   3) The reviewer should examine and verify that the data analysis and source code are accurate.

l. Evaluate whether adequate sensitivity analysis has been provided. Have the most important variables in the model been identified? Has an important variable been

left out? Has the impact of including or excluding scientific studies or other data been adequately explored? If so, the reviewer shall provide an alternate approach or application for sensitivity analysis and/or identify those parameters that should have been included.

The appendices include much of the raw data being modeled and I do not have the expertise to critique these. However, I am concerned that EID is a good measure for human infectivity (or at least the best measure). Page 40 indicates that EID rather than PFU or ID/LD was chosen but the explanation is not given (maybe more available data). The DR model is key to determining the number of illnesses resulting from consumption of poultry or eggs and as stated on page 59, there is great uncertainty in the intranasal mouse model being applicable for humans. I assume from Figure 6 that the Schijven et al model was chosen for the FSIS assessment (page 61), although this is only specifically stated on page 10.

Response 184

EID50 is the best choice, in part because it is the only choice, as all HPAI level data identified in poultry meat and eggs were measured using EID50s. In addition, most of the potential dose-response data were also done measure the dose in EID50s. The only requirement is that both the exposure and the dose-response are in the same units. The dose-response used in this version of the risk assessment was that from a human AI intranasal exposure trial conducted to evaluate human susceptibility to AI (Beare and Webster, 1991). See Section 5.

Comment 185

m. Comment on the adequacy of the risk assessment model documentation. Is the report clearly written? Is it complete? Does it follow a logical structure and layout? Is it useful? If not, the reviewer shall provide an alternate outline and/or approach for adequately and clearly documenting this risk assessment.

Comments on the completeness and clarity of the document are made separately. There are places in the document that need amplification or better explanation and a glossary would be useful if the terms are not explained in the text when the terms first appear.

Response 185

The text was searched and as terms first appear they were explained. A glossary has not been added.

Comment 186

n. Evaluate the approach taken to estimate illnesses due to consumption of HPAI. Does the data derived from the animal model provide a sufficient surrogate upon which to estimate human illnesses? Are there additional methods to better utilize these or other data? If so, what additional approach should be taken?

No model is perfect and most risk assessments rely on models not exactly designed for the pathogen/food combination under study. A research goal is to develop a better one. However, I am a little concerned about EID being used as a level of contamination. It is not clear from the text how well this relates to diseased poultry or non-fertile eggs. A clear rationale should be given even if this is the only animal model that is available.

In summary, this is an important assessment to do, although it is very possible no human illnesses will ever occur from US flocks in the near future, and the data are very uncertain. This should be a stimulus to carry out research to fill the gaps and determine what the risk is more likely to be.

Response 186

As the reviewer suggests, we have developed an alternative dose-response based on an AI human intranasal study, see Hazard Characterization, Section 5. These data are more biologically relevant to the mouse model, though they are limited.

See Response 184. The EID50 methodology is simply being used as a measure of the number of active virus particles within poultry meat and eggs. The only assumption is that the methodology is consistent within and among laboratories.

Annex: Risk Assessment of AI in poultry, shell eggs and egg products

Comment 187

Purpose of the model is not to predict the absolute number of illnesses, yet risk management question is to determine the risk of human illness from consumption of these products (page 10 vs. page 12). Maybe a secondary goal is to suggest areas for research and surveys since the number of predicted cases requires more research (page 12).

Response 187

The text has been changed to “However, the primary purpose of the model is not to predict the absolute number of illnesses, especially given that further research is needed.”

Comment 188

Mandate
The could be more background into cases of the illness in developing countries; no studies from any of these countries where illnesses and deaths have occurred are quoted, since on page 15 the assessment is focused on HPAI strains which have caused illnesses and deaths in SE Asia. The pathways listed on page 25 as well as eating products could have contributed to the illnesses and deaths. Are there any epidemiological studies from outbreaks to help us?

Response 188

There are no epidemiological studies that can help in terms of attributing illnesses to consumption of HPAI besides the incidences of consumption of duck blood. Even then, proximity to live or dead HPAI-infected birds cannot be ruled out. The reviewer is correct that for most cases, the source of the HPAI exposure is unknown. For those where the source is known, consumption of contaminated products has not been associated with HPAI illness or death.

Comment 189

Page 21, second para; page 29 Table 2, and elsewhere: Strain H7N7 is quoted a few times relating to illnesses in the Netherlands. Yet, it is excluded from this assessment.

Response 189

See Response 179.

Comment 190

Page 21 and elsewhere. The recent poultry outbreak in the UK is worth examining because there were delays in notification (possible traceability issues from imported birds and a large company trying to sort out the problem of dying birds without informing the government soon enough).

Response 190

See response 178.

Comment 191

Page 23: section on stomach acidity: I am not sure what recent meals means. Acidity is not as high if an individual eats quickly after a period of fasting, e.g., one meal a day; also intake of larger quantities of liquid like water or other drinks will dilute out the acidity and facilitate the passage of pathogens to the intestine.

Response 191

The text has been changed to "However, many biological factors can change individual responses to the virus such as gastric pH alterations due to age, presence of ulcers, antacid use, medications (*e.g.,* H_2 blockers), and the content of recent meals."

Comment 192

Page 26 and 27: Combinatorial approach will be new to many readers. This is to be described below (second para on page 26), but this is not clearly done. Probably the second para on page 27 is the closest but more could be done.

Response 192

See response 173.

Comment 193

Table 2: The data used are means mostly from industry representatives or unpublished data. The table is useful as it does summarize the inputs and gives assumptions. However, I think it would be useful to the reader to also see the range of the data points.

Response 193

Table 2 is simply a summary of the data. The full distributions of data are given in Appendix B.

Comment 194

Contact rate (page 29) depends on one bird infecting 32 others based on the H7N7 outbreak. I would like as little more explanation how this progresses. There will be an acceleration of infected birds as each infected infects 32 others, but later this will slow as there are fewer to infect, e.g., 50% of the contact birds are already infected. Also, as the disease progresses, the symptoms of the first birds may increase or decrease the likelihood of contact (listlessness my mean less social activity). This is discussed further on page 37 where 10 birds are the contact rate and a range of 1-64 is given. I am not sure how the baseline scenario of 8 birds every 6 hours is derived?

Response 194

The baseline scenario indicates the 1 infected bird can infect 8 susceptible birds. Each of these 8 birds, given a latency period, can infect another 8 susceptible birds. This progresses until there are no more susceptible birds to contact. This process will not slow, but rather result in 100% of the surviving bird population now being infected. The reviewer is correct that issues of social activity may result in non-linear relationships. These have not been addressed in this risk assessment.

Comment 195

Page 30. I am not clear what average 75% dressing % (and similarly elsewhere) means as written (I assume in this example once birds are eviscerated and organs taken out they lose 25% of their weight) – they way the text is written is not clear to me.

Response 195

The reviewer is correct that the meaning of dressed weight is the mass of the carcass following processing. The text has been changed to reflect that a 70% dressed weight is being used for chickens in the model.

Comment 196

Page 31: what does purge and EID mean? (EID later is shown to be embryo infectious dose but this is the first time use). There are enough examples of terms used for non-poultry experts that a glossary should be considered.

Response 196

See Response 186. At the first use of "purge" the following text has been added: "associated liquid with packaged chicken".

Comment 197

Page 31, 6th column: portion is used as data required but a value is given (5.4 log); a portion to me means a percentage.

Response 197

The text has been replaced with a percentage.

Comment 198

Pages 33, 35, Production model: the assumption is that mortality is the major trigger to recognize an HPAI flock outbreak. Yet, on page 21 distinctive symptoms are also given before death in 3-4 days. And on page 38, Table 4 lists morbidity. Are poultry mangers not aware of symptoms, at least enough to start monitoring for early deaths? On page 39, last para, …by 24 hrs post infection, 90% of the birds demonstrate infection although these data are difficult to model. (However, the UK story in January illustrates the other cases where deaths are noted but action may be delayed). So, I assume this a conservative approach to consider mainly mortality. By the way, in that paragraph (5 lines from the bottom) "demonstrate demonstrable" infection is stated, but what does demonstrable mean if not visible (apart from the English where the two words side by side is almost tautology)?

Response 198

The reviewer points out that there are data describing the signs of HPAI illness every six hours. These data were not used in this risk assessment

as signs of HPAI are not necessarily descriptive of HPAI as compared to other diseases and not may be a good indicator if poultry managers are not "looking for" HPAI. It must be remembered that this risk assessment addresses the risk from the index flock. Certainly if HPAI was known to be in surrounding areas or recently identified in the U.S., poultry managers may be able to identify a flock with HPAI sooner than the index flock. However, the risk assessment does not address this.

The following section has been added to discuss the issue of mobidity: "The probability that a flock is sent to slaughter is based on using 0.5-2.0% daily bird mortality as an indicator for identification of a flock and subsequent holding. Other means of identifying a flock as HPAI-positive, such as morbidity or reduced feed/water intake are not addressed in the baseline model. Percent daily morbidity is not used for the following reasons: HPAI, in general, is not pathognomonic and therefore clinical signs may be confused with other non-notifiable poultry diseases (Elbers et al., 2005; 2007). Swayne and Halvorson (2003) report, "Clinical manifestations vary depending on the extent of damage to specific organs and tissues (*i.e*., not all clinical signs are present in every bird). In most cases in chicken and turkeys, the disease is fulminating with some bird being found dead prior to observance of any clinical signs." Furthermore, unpublished morbidity data from infecting 10 chickens with H7N7 showed 2 birds with general sign, 6 with non-specific signs, and 2 with no signs 24 to 48 hours before death (J. van der Goot, personal communication). These data suggest that the majority of infected birds did not show specific signs of HPAI prior to death. In addition, detection of signs is a subjective measure and is likely variable.

"Demonstrable" has been replaced by "visible signs of".

Comment 199

Page 36, 3rd para: add "respectively" after ..20 weeks in a house;..

Response 199

Text has been changed.

Comment 200

Table 3: what do light, medium and heavy mean? Are these bird weights for marketing?

Response 200

Yes, this is just a descriptor for bird weight. Text has not been changed.

Comment 201

Page 40: this is where some definitions are given like EID. However, it is not clear to me what EID has to do with poultry and poultry meat. Are ID_{50}, LD_{50} and PFU used in this doc? If not do we need them?

Response 201

EID50 is the method by which the level of HPAI in poultry meat or egg contents is determined. EID50 is also the metric by which that level is described, for example, EID50/mL. The other methodologies and metrics listed above are not directly used, however, data presented in the following table use these measurements and they therefore should be described. The text has not been changed.

Comment 202

Table 5: are the titers mean values in some of the docs quoted (a range is given for some of the data bases)?

Response 202

It is unclear if the values are means. The following is a quote from Swayne and Beck, 2005 "In the current study, the level of virus detected in skeletal muscle varied with HPAI virus strain; i.e., H5/HP/83 and H5/HP/03 had 102.7–3.2 and 107.3 EID50/g of breast or thigh meat, respectively."

Comment 203

Page 41, 2nd para: consumer storage is not considered important because the virus does not grow but please indicate the likelihood of die off.

Response 203

No scientific research was identified to specifically address the rate of die-off for HPAI. However, several studies investigating rates of virus decay in different mediums have been identified. See Response 125 for a summary of the results.

Comment 204

Fig 4 should precede Table 6 on Page 42, and I think this can be done by reducing its size slightly.

Response 204

Figure 4 was moved.

Comment 205

Page 43 What does heuristic mean? One definition states: speculative formulation serving as a guide in the investigation or solution of a problem. However, a different term or wording would be better for the reader.

Response 205

The text has not been changed.

Comment 206

Page 44, 2nd para: Clarify for the reader that chlorine has different effects on LPAI and HPAI. The text certainly gives the impression that chlorine as used by the industry does not destroy the HPAI.

Response 206

The data suggest that the level of chlorine used under the conditions of this experiment do not have a significant effect of the level of this particular HPAI strain. The text has been changed to the following "No significant change was observed for HPAI, suggesting that under these experimental conditions, chlorine can be effective against LPAI but not HPAI".

Comment 207

Table 7: what does EDI stand for? If Estimated Daily Intake I am not sure that is valid since meal size and frequency is more realistic for pathogen intake unlike nutrition which depends on food being consumed over a period of time.

Response 207

EDI stand for Estimated Daily Intake. The reviewer is correct. See Response 21.

Comment 208

Page 45: 1st para: The sentence " The risk posed from egg type birds is in the eggs which could have been…. Apart from having similar words follow one another, the risk is not in the eggs. This can be better expressed.

Response 208

The text has been changed to "In this case, the risk is posed by eggs produced by an HPAI-infected flock, where those eggs were laid before the flock was diagnosed".

Comment 209

Page 46: Pasteurization is effective in destroying bacterial pathogens, e.g., *Salmonella* only if the load is reasonably low. Very high levels will allow some survivors. This may be the same for virus although growth will not subsequently take place. So, before egg products are completely ruled out as vehicles for the virus, check on possible maximum load and D-values achievable under normal pasteurization conditions.

Response 209

The risk assessment does not conclude that egg products should be ruled out. The conclusion of the risk assessment is the egg products are of lower risk than poultry and shell eggs. The following text is in the report: "Data from USDA's Agricultural Research Service show that FSIS time/temperature recommendations for egg products processing are sufficient to inactivate HPAI (Swayne and Beck, 2004). Only dried egg whites processing may not completely remove HPAI; however, the process of preparing dried egg whites requires a minimum of 7 days. It is likely that the hen flock that produced the contaminated eggs would have been identified as HPAI-positive before the process is completed alerting egg products processors to the problem. Given the lower risk associated with these products compared to poultry and shell eggs, the model currently does not assess egg products."

Comment 210

Page 47, 3rd para: I am not sure where contact rate of 2 comes from (expert opinion, guess?).

Response 210

The text has been changed to "Hens are typically caged during their egg production life cycle. Given the reduced bird-to-bird contact, it is possible that HPAI-infected caged birds would spread the virus more slowly compared with non-caged or ground raised meat-type birds (Elbers et al., 2004; 2006, 2007). To estimate the rate of spread of HPAI among caged birds the data from HPAI infected caged layers (Elbers et al., 2007) were used (see Production Module, contact rate). An effective contact rate of 2 is assumed in the baseline scenario (Figure below).

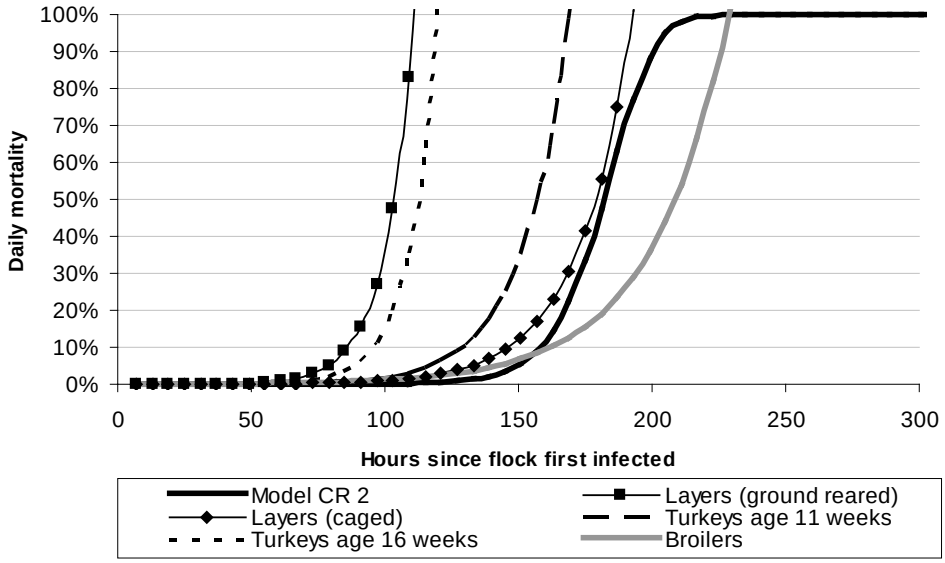


Figure. Percent daily mortality as predicted by the model at an effective contact rate of 2 compared with 2003 H7N7 HPAI Netherlands outbreak data (based on 55 caged layer flocks).

Comment 211

Page 48, 4th para: the drop in production is not modeled; this gives a more conservative approach.

Response 211

A drop in egg production is not a forgone conclusion for HPAI and was therefore not part of the baseline model. To address the reviewer's comment, data from Bread et al., 1984 was used to model a drop in egg production. The following text has been added: The risk assessment can be used to evaluate the impact of different data by developing scenario or what-if analysis. For example, 25 white leghorn hens were inoculated via intranasal and the conjunctival sac with a strain of H5N2 identified during the 1983 Pennsylvania HPAI outbreak (Beard et al., 1984). This strain is described as highly pathogenic or pathogenic depending on the testing method. The rate of mortality caused by this H5N2 strain is different compared with the mortality data that is considered representative of H5N1 in this risk assessment (H5N1 mortality within 36-42 hrs compared with a minimum of 96 hours for H5N2); however, scenario analysis can be performed by asking "what would be the impact of an HPAI strain that resulted in the following flock characteristics (Table 25)?"

Table 2. Characteristics of H5N2 experimental study in hens

Days post-inoculation of H5N2	Clinical signs	Dead	Eggs total	HPAI+ eggs	Thin/soft shelled
2	1	0	14	0%	
3	23	0	14	86%	3
4		16%	3	100%	2
5		48%	0		
6		72%	0		
7		76%	0		
10		80%	0		
11		84%	0		
12		88%	0		
20		92%	0		

The effect of replacing the baseline data with the data in Table 25 (columns 1, 3-5) are given in Table 26. The uncertainty in the data can also be reflected by further scenario analysis (columns 3-6, Table 26)

Table 3. Results of scenario analysis using Beard et al., 1984 data

Previous hours of egg production once flock is identified as HPAI-positive	Beard data	Beard data assuming eggs can be contaminated 24 hrs earlier	Beard data assuming eggs can be contaminated 48 hrs earlier	Beard data assuming egg production drop 24 hrs later	Beard data assuming egg production drop 48 hrs later	Current baseline
Past 24 hours	0[1]	0	0	0	0	9,431
Past 48 hours	0	0	0	0	0	1,602
Past 72 hours	0	0	0	0	170	224
Past 96 hours	0	0	0	21	49	31

Past 120 hours	3	26	214	6	6	4
Past 144 hours	1	7	61	1	1	1
Past 168 hours	0	1	8	0	0	0
Past 192 hours	0	0	1	0	0	0
Past 216 hours	0	0	0	0	0	0
Past 240 hours	0	0	0	0	0	0
Past 264 hours	0	0	0	0	0	0
Past 288 hours	0	0	0	0	0	0
Past 312 hours	0	0	0	0	0	0
Past 336 hours	0	0	0	0	0	0
Sum HPAI+ eggs	3	34	284	28	226	11,293

[1] Numbers indicate HPAI-positive eggs. Numbers do not include HPAI-positive eggs that are removed due to visible deformities.

The risk assessment predicts very few exposures compared to the baseline scenario for the following reasons: 1) a drop in egg production limits the number of HPAI-positive produced (egg production drop is not being modeled in the baseline), and 2) HPAI-positive eggs are not produced until 3 days post-infection (baseline model allows for 15% of eggs to be HPAI-positive by 6 hours post-infection).

These data suggest that a drop in egg production would be the key to identifying an infected hen flock *with these characteristics* as positive, and not mortality. The transmission model estimates the number of susceptible birds (not infected) over time and can be used to estimate the number of non-HPAI positive eggs (0.7 eggs/hen/day). There is about a 30% drop in egg production by 5 day post-infection suggesting that if this was enough to alert flock managers to the problem, then the flock would stopped at ~5 days (127 hours, see stared line at 70%, Figure below) compared with 9 day (as predicted by the mortality data based on the Beard study; ~216 hours, see hatched line at 2%).

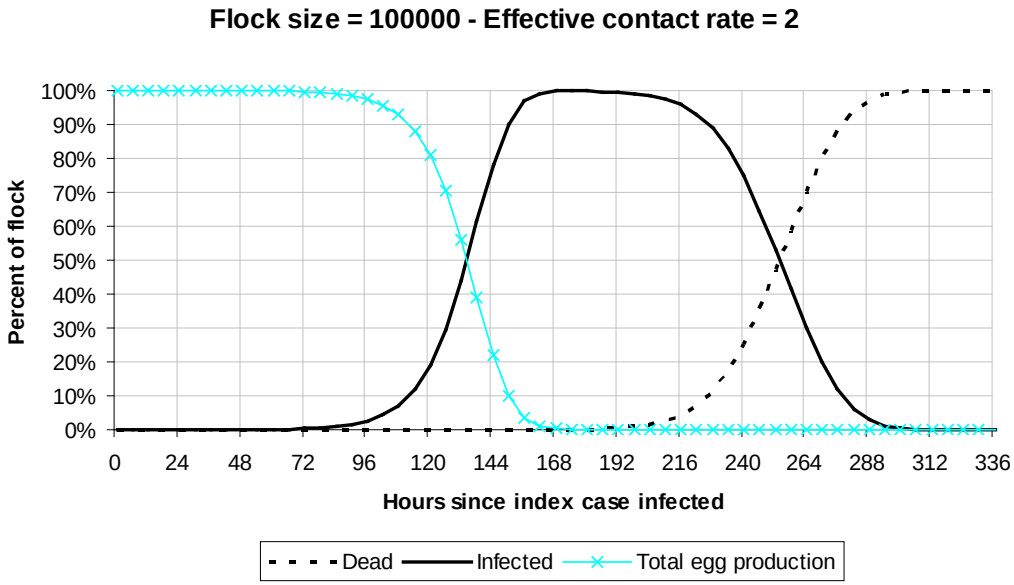


Figure. Total egg production, infection, and mortality of a hen flock based on Beard et al., 1984 data.

Comment 212

Page 49, Table 8 and para 5: how valid is EID when there are no embryos in table eggs?

Response 212

The reviewer appears to be confused given that the definition of EID50 was not previously clear. See Responses 186 and 210.

Comment 213

Page 51, last line: is 4.9 log/ml the absolute maximum or could it go higher – important for inactivation studies?

Response 213

The level of HPAI in internal egg content could be higher as evidenced by Bean et al., 1985. This study showed that internal contents of eggs could have approximately $10^{5.6}$ EID_{50}/mL. However, this egg was sampled at the time of the bird's death. Eggs laid by birds at different stages of infection will likely have lower levels of HPAI. Therefore, if a flock produces multiple infected eggs there is likely to be a distribution of HPAI levels.

Comment 214

Page 54, as for Table 7, in Table 12, what is EDI (estimated daily intake?)?

Response 214

EDI stand for Estimated Daily Intake. See Response 21.

Comment 215

Page 57, last line: this section seems to stop without a conclusion indicating what approach is being taken for DR in this assessment.

Response 215

The Hazard Characterization has been rewritten to incorporate the additional work that was done. Section 5 now specifically says which dose-response is being used in the baseline model.

Comment 216

Page 59, Table 14: footnote. EID_{50} =Embryo Infectious Dose 50%, MID_{50} = Mouse Infectious Dose 50%, $TCID_{50}$ = Tissue Culture Infectious Dose 50%, and PLU = Plaque Forming Units.

Response 216

Text has been changed.

Comment 217

Page 60, Figure 6: …. $r = 10^{-4}$ and 10^{-6}, **respectively**.

Response 217

Text has been changed.

Comment 218

Page 61, Table: number missing 14a/15; 14 already used; what is the relevance of vaccine trials in the section (5.3.1) since these are not mentioned in the text? Section 5.3.2 discusses vaccines.

Response 218

Table numbers have been changed.

Comment 219

Page 62, 3rd para: what does CBER stand for?; Table without a number (14b?); should ah substitute for avian in column 4 since in the text ah = avian?

Response 219

CBER stands for "Center for Biologics Evaluation and Research". Text has been changed to reflect this. "Avian" has been changed to "ah" in table text.

Comment 220

Page 63, footnote na = data unavailable from abstract – how about a phone call and a personal communication to get this data?

Response 220

Unfortunately, we could not find what the reviewer is referring to.

Comment 221

Page 64, 1st para: what is the rationale for a 6-hr interval?; 3rd para: detection is associated with mortality only; even if a conservative approach is taken, is it worth mentioning that some flocks would be stopped on the basis of unusual symptoms and a few dead birds; also on page 66 1st para?

Response 221

See Responses 136 and 158 and Response 198.

Comment 222

Page 65, Tables 15 and 16: what is ind serv? If this is individual servings, some text explanation should be added. Is EID_{50} appropriate for adult birds?

Response 222

Text has been removed. EID50 is the appropriate matrix. See Responses 186 and 210.

Comment 223

Page 67, 2nd para, line 2: …consumption of contaminated chicken [add] **and turkey**.

Response 223

Text has been changed.

Comment 224

Page 67 last para and 68 1st para: what is the rationale for averaging the results (796 and 1214) from the different rows based on hours flocks are infected, and then discussing the effect of cooking on these? What about the more risky scenarios > the average? I understand the combinatorial approach selects a baseline; are these averages a part of the baseline?

Response 224

The rational for averaging the 6-hour time intervals at which a flock would not be identified as HPAI-positive and be sent to slaughter is to use this average for mitigation scenario analysis. Tables 21 and 22 give the worst case scenarios based on when a flock could randomly be infected. To see the impact of a particular mitigations strategy, such as increase consumer cooking, one can use the model to generate those results. The results in the risk assessment report the general trends observed.

Comment 225

Page 70, Fig 8: how do we square " an additional 4 cases" in para 3 with the Figure, which shows cases between about 100 and 106? Also, although the Figure shows a 6.4 $logEID_{50}/ml$, this is not in the text, only "If the level in the purge is higher…"

Response 225

The y-axis for Figure 9 was incorrect. The figure has been removed and replaced with the following text: "At the fraction HPAI is assumed to be cross-contaminated (~0.53%) from poultry and subsequently ingested (see Section 4.4.5.4 "Poultry Preparation Module, Cross-contamination"), cross-contamination of HPAI is not a significant source of human illnesses in comparison to the number of predicted illnesses from direct-consumption. On average, an increase of approximately 2.5% in the estimated average number of illnesses is predicted. However, this is likely an overestimate. The model does not allow the user to specify what fraction of servings is cross-contaminated[3]. Therefore, all HPAI-positive servings are assumed to result in cross-contamination for this scenario analysis. Furthermore, 100% of the cross-contaminated virus is assumed to be consumed. In reality, only a portion of the virus would likely be cross-contaminated to a surface, and then only a sub-portion would then be transferred to a food not likely to be cooked."

Comment 226

Page 73, 1st para: add (6.3) after "Effect of Uncertainty".

Response 226

"Effect of Uncertainty" has been changed to "Sensitivity Analysis".

Comment 227

Page 73, 2nd para: Table 2 doesn't have much on the assumptions for the egg scenario. List all the assumptions together, either in Table 2 or nearer to the text here.

Response 227

Table 2 has been modified to include all major egg model assumptions.

Comment 228

Page 80, 2nd para: "lowers the probability" add "marginally" from the data shown in Table 26.

Response 228

[3] An analysis to estimate the frequency of cross-contamination events during preparation poultry was not attempted. Therefore, when this component of the model it turned on, all serving are assumed to result in cross-contamination. The impact of this assumption is proportional. For example, if 25% of consumers are expected to cross-contaminate during poultry preparation, the number of predicted illnesses due to cross-contamination will be a forth of that predicted by the model.

We respectfully disagree with the reviewer. There is no need to qualify the statement.

Comment 229

Typos
Page 23, 2nd para, line 7: word missing – "however (**it/they/the virus**) could survive.."
Page 35, 1st para: HAPI twice. = **HPAI**
Page 44: 2nd para: **fro** presumably for.
Page 51, 3rd para: However, some eggs could **be**16-20 days…
Page 54, 3rd line: **completed** instead of comleted.
Page 61, Table: Relevant phisiology = Relevant **physiology; trials** instead of trails.

Response 229

Thank you for corrections. All have been addressed in the report.

Comment 230

Data on the Upper Holton, Suffolk, UK H5N1 turkey outbreak on January 27 2007 (http://www.oie.int/eng/info_ev/en_avianinfluenza.htm).

Affected animals

Species	Susceptible	Cases	Deaths	Destroyed	Slaughtered
Birds	159000	7000	2500	152000	0

Outbreak statistics

Species	Apparent morbidity rate	Apparent mortality rate	Apparent case fatality rate	Proportion susceptible removed*
Birds	4.40%	1.57%	35.71%	97.17%

* Removed from the susceptible population either through death, destruction or slaughter

Response 230

See Response 178.