PEER REVIEW REPORT

Responses to Comments from

External Peer Review (Letter) of FDA-iRISK® Model and Associated Library of Commodity/Hazard Combinations – Chemical Hazards

June, 2015

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I. INTRODUCTION

FDA-iRISK® is a web-based system designed to analyze data concerning microbial and chemical hazards in food and provide an estimate of the resulting health burden on a population level. FDA-iRISK estimates risks for chemicals and pathogens based on the food and its associated consumption data and processing/preparation methods, the hazard and its dose-response curve, and the predicted health effects of the hazard when ingested by humans.

FDA previously conducted a peer review (peer review I) of an earlier version of the FDA-iRISK model in December 2010. The first review focused on the model structure for microbial hazards and risk scenarios for microbial hazards. This second peer review of FDA-iRISK, conducted in the spring of 2013, evaluates the conceptual framework for the model, assesses the usability of its interactive interface with a focus on chemical hazards and microbial toxins, and reviews example scenarios for chemical hazards. For this peer review, five experts were selected to evaluate and provide written comments on the FDA-iRISK model 1.0, the FDA-iRISK Technical Documentation 1.0, and the user-friendly aspect of the web interface.

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II. CHARGE TO REVIEWERS

The focus of this review is on chemical hazards. FDA conducted a peer review in 2010, with a focus on microbial hazards, for the beta version of FDA-iRISK. Where appropriate, the reviewer is encouraged to comment on chemical hazards as well as microbial hazards (in particular new or improved features and functions resulting from efforts to expand the capacity of FDA-iRISK and enhance the user interface as suggested by the first peer review panel). If a charge question is outside of a reviewer's areas of expertise, the reviewer should simply note it as such.

Charge Questions:

1. The FDA-iRISK model estimates risk and generates ranking of food-hazard pairs through a pre-determined model structure consisting of seven elements requiring user-supplied data and information: the food, the hazard, the population of consumers, process module describing the introduction and fate of the hazard up to the point of consumption, consumption patterns, dose-response curves, burden of disease metric. Is the overall modeling approach fundamentally sound for the risk ranking purpose and scope? If not, what problems exist and how should they be addressed?

2. The FDA-iRISK model structure consists of a process module that enables the user to define initial conditions and select from among nine process types to describe changes in the prevalence and level of a hazard, as well as the unit size of food, at various process stages.

    2.1. The initial conditions specified in a process model include prevalence, concentration, and unit size (a fixed quantity of food, for example, the quantity of a consumer package or production batch). Are these characterizations of initial conditions appropriate and are they implemented appropriately in the model? If not, the reviewer should suggest how the characterizations might be improved.

    2.2. Are the process types in the model adequate to describe major relationships or outcomes at various process stages for the food-hazard pairs? If not, please explain.

    2.3. For microbial toxins where the process model would start with a microorganism in food while the hazard in the food at consumption would be a toxin, are the process types in the model adequate to describe major relationships or outcomes at various process stages involving microbial toxins? If not, please explain.

    2.4. Are there additional process types that should be incorporated into the model for chemical hazards, microbial hazards, or microbial toxins? Is there any process type or function currently in the model that is not necessary and should be omitted for chemical hazards? If so, the reviewer should explain how to address such changes in the model.

3. The technical document provided for the peer review describes the functions or equations (Equations 1 through 46) that underlie exposure assessment and risk characterization for chemical and/or microbial hazards.

3.1. Are any of the assumptions underlying these functions or equations (described in the technical document) unreasonable according to current modeling in which estimates of risk are generated? If so, please explain.

3.2. Are these functions or equations scientifically justified and biologically/ toxicologically sound for the purpose they are used in the model?

3.3. Considering the several food-hazard pair examples provided, are the equations or functions accurately implemented in the model? If not, please explain.

3.4. The technical document describes two new features: "positive distributions" and "stability analysis." Are these features adequate to address the intended computational or model convergence issues? If not, please explain.

4. A key feature of FDA-iRISK is the ability to compare both chemical and microbial risks. The model reporting includes results with different metrics. In addition to the mean risk of illness and the total number of illnesses, the annual DALY is used. With this in mind:

4.1. Comment on the appropriateness of using the annual DALY and the strengths and limitations of the implementation of this metric in the model for chemical hazards.

4.2. Comment on the appropriateness of available options for microbial and chemical dose response functions in the model and how they are used, as well as other dose response functions for chemical or microbial hazards that might be included as templates.

4.3. Overall, are the results generated appropriate for comparing chemical (acute and chronic exposures) and microbial risks and risk ranking purpose? If not, the reviewer should explain other results and/or analyses that are needed.

5. Given that the primary purpose of FDA-iRISK is ranking risk among a number of food-hazard pairs:

5.1. Is variability adequately characterized in the model? If not, please explain what changes might be considered to improve characterization of variability. Comment on other probability distributions (if any) that might be added as templates to characterize variability for exposure from chemical or microbial hazard.

5.2. Comment on the appropriateness and adequacy of how consumption is defined for acute versus chronic chemical exposure. Considering how consumption is defined for chronic chemical exposure, to what extent (if any) the exposure might be over or underestimated? If so, the reviewer should explain what changes might be considered to improve the consumption estimate to be more consistent with current modeling practices in which estimates of risk are generated while balancing the need for broad risk ranking using the annual DALY.

6. The FDA-iRISK Monte Carlo simulation is designed to address variability, and uncertainty can be explored by scenario analysis. Given the practical constraints of the model and data, a sensitivity analysis option will be provided by which the user can change parameters or distributions in the model inputs and obtain ranked results as compared to the original scenario. If this approach is not sufficient, please provide additional or alternative approaches and explain what changes might be considered and how they would improve the model.

7. Comment on the FDA-iRISK user interface. Is the interface user friendly? Are there any features that should be modified or added to facilitate ease of use? For example, is there sufficient description in the user interface to understand each component of the model?

8. Comment on the adequacy of the model documentation features within FDA-iRISK. Can the user accurately document data sources and confidence in the model?

III. FDA RESPONSES TO INDIVIDUAL REVIEWERS COMMENTS

In the following sections, FDA's responses to individual comments from the reviewers are organized according to the sequence of the charge questions, i.e., general impressions followed by questions 1 through 8. Comments from all five reviewers were itemized and listed under each charge question. Where needed, some of the comments were edited to protect anonymity of the reviewers. The individual comments and responses were further grouped into three categories:

Noted Strengths:
Comments agreeing with the approach taken by FDA and noting the strengths of the FDA-iRISK tool. These types of comments generally require no further action from FDA.

Short-Term Action Items:
Comments requesting FDA to make quick or necessary changes, e.g., clarifying scope, terms, formulas, etc.; fixing errors; addressing discrepancies that undermine objective, use, or clarity. Also includes comments not requesting any immediate or needed changes, but expressing concern, confusion, or criticism. These types of comments generally require a response in the form of the rationale behind FDA's chosen methods, tool capabilities, intent, etc.

Longer-Term Action Items:
Comments requesting FDA to make changes that may require a longer-term effort or further consideration of how the suggestion fits into the tool's goals and intended use, e.g., enhancing usability of tool through various augmentations or linkages to databases; expanding scope to include metabolism, aggregation, probabilistic uncertainty analysis, etc.; or incorporating additional modeling components or capabilities. Also includes comments requesting FDA to make changes that may be beyond the scope of the review or beyond the present scope and/or intent of FDA-iRISK, such as incorporation additional modeling components to address metabolism, and exposure from multiple foods and aggregation.

Of note, in the following sections, FDA provided responses to individual comments from the five peer reviewers, i.e., the responses were specific to the peer reviewers' comments specific to the FDA-iRISK model 1.0, the FDA-iRISK Technical Documentation 1.0. In addition to these responses, FDA has continued to develop the tool based in part on comments and suggestions from both the first and second peer reviews. As an outcome of these efforts, in March 2015, FDA made available FDA-iRISK 2.0 that includes enhancements and new capacities for the underlying modeling methods and equations, user interface, and data sharing and reporting. FDA-iRISK 2.0 (the tool itself) and related materials are available at http://foodrisk.org/exclusives/fda-irisk-a-comparative-risk-assessment-tool/. Specifically, the technical document for FDA-iRISK 2.0 is available at https://irisk.foodrisk.org/Documents/FDAiRISKTechnicalDocumentation.pdf.

GENERAL IMPRESSIONS: COMMENTS AND RESPONSES

Noted Strengths:

[**COMMENT G-1-1**] It is the understanding of this reviewer that this tool has been developed to: 1) permit the ranking of risks posed by all hazards (acute and chronic chemical, microbiological and microbial toxins) in foods; and 2) provide a meaningful platform to share these risk rankings among risk assessors. The reviewer was provided with technical documentation, a workbook, and three case studies (two acute chemical hazards, one chronic microbial toxin). Of the three scenarios, histamine in raw tuna had the highest DALY score (222), while ammonia in frozen pizza had the lowest DALY score (0.262). This qualitatively makes sense, as histamine contamination of fish is reasonably common and the threshold for human health effects is reasonably well-documented. Fish is highly consumed and so it makes sense that this should have a high DALY score. On the other hand, ammonia contamination from refrigerant leaks is rare; levels high enough not to be detected by smell and potentially resulting in resulting in illness are even rarer. It makes sense that this would have a low DALY score.

[**COMMENT G-1-2**] The user-interface is relatively straightforward and provides the user with well-explained options. The scenario-ranking report tool provides an easy-to-read and digest means of examining the model outputs. The model summary report provides good information about the user-defined inputs and that facilitates peer review of the model outcomes. The software allows the user much flexibility and full control of what information to input (this can also be a disadvantage, as there are no fail safes). The user can document the sources of data or assumptions made.

RESPONSE: FDA thanks this reviewer for their comments.

[**COMMENT G-1-3**] I presume that the accuracy of the information provided refers to all the inputs used for the three case studies. This reviewer used the files generated in the training session as well as all other available scenarios and model summary reports available in the iRISK tool. This allowed this user to trace the references and sources for a lot of the information inputs. The information used is well-documented from peer reviewed literature or FDA internal documents.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT G-2-1**] My overall impression of iRISK has not been changed since 2010: iRISK is a very useful and well developed tool for risk assessment. It has a logical structure and, for a user with experience in risk assessment, it is easy to use. For a user without such experience, it may be difficult, but it should be like that just because you shouldn't do risk assessment without proper training/experience. The documentation is clear. I experienced only small problems when exploring the model. I intend to start using iRISK in my teaching; it seems to be well suited for that purpose. I will also propose some of my colleagues to start using it.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT G-2-2**] The focus of this second review is on chemical risk assessment, which is not my main expertise. I would not be surprised if the modular approach used in iRISK is not

intuitive for chemical risk assessors. In my experience, this "process modelling" approach is typical for microbiological risks, but not so much for chemical risks. I do, however, see no reason why this approach would not be suitable in general.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT G-3-1**] *General Impressions of the iRISK System:* iRISK is a very useful tool, implemented in a clear logical way. I would not call iRISK "user friendly" because it does require a knowledgeable user to develop informative risk scenarios. It is user-intensive and necessarily tedious to develop scenarios. I think it will be a very valuable system for food safety risk assessment because both chemical and microbial hazards can be modeled.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT G-4-1**] U.S. FDA should be commended for supporting the development and deployment of a publicly available and easily (web) accessible interactive "risk ranking" system such as iRISK.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT G-4-4**] In fact, the IOM/NRC 2010 Report states that, among the methods it compared, iRISK was "[c]losest to the standard risk assessment paradigm." Indeed, FDA-iRISK considers seven essential elements of the risk assessment system, i.e., three independent/primary elements (Hazards, Foods, Population Groups) and four dependent/derived elements (Food Production and Process Models which depend on both the Foods and the Hazards; Consumption Models, which depend on both the Foods and the Population Groups; Dose-response Models, which depend on both the Hazards and the Population Groups and are "informed" by the Process Models and Consumption Models; and Health Metrics, which depend on the Dose-response Models and the Population Groups). Though currently there are available models that treat each of the above elements in a much more comprehensive and advanced manner than the corresponding components of iRISK (see e.g., references in the selected bibliography provided at the end of the present review), there is nothing similar to iRISK in terms of *integration, accessibility, and ease of use.* By offering a "one-stop-shopping" approach for the entire exposure-to-effect sequence, FDA-iRISK has the potential of becoming a widely used and widely useful tool.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT G-4-6**] Actually, the model presentation that took place on February 26, 2013 was an example of the potential of less than optimal application of the FDA-iRISK model. Though the meeting was superbly organized and it was overall both informative and productive, the presentation of FDA-iRISK focused mainly on the "mechanics" of interface usage, putting an emphasis on how easy it is to use the model rather than on how one can assure the use of the best possible science within the limitations of this particular modeling system. So, the examples that were used in the demonstration were unfortunately not as effective as they could be, due to the

adoption of oversimplifications in the selection of modeling options and parameterizations for the problems considered (as discussed in more detail below, in the answer to Question 3.3).

[**COMMENT G-4-7**] As an overall conclusion and recommendation of the present review, it can be stated that iRISK has great potential.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT G-5-1**] FDA-iRISK is a web-based system designed to analyze data concerning microbial and chemical hazards in food and to provide an estimate of the resulting health burden on a population level. This peer review of FDA-iRISK evaluates the conceptual framework for the model and assesses the usability of its interactive interface with a focus on chemical hazards. Two written documents were provided for the review: 1) "iRISK 1.0 Technical Documentation," February 2013, and 2) "Workbook for Peer Reviewers – Implementing Chemical Risk Scenarios in iRISK." In addition, a one-day workshop was held to familiarize peer reviewers with the model software via a power point presentation of the FDA-iRISK model version 1.0 and hands-on exercises with the web-based tool.

[**COMMENT G-5-2**] In general, the overall model construction of iRISK is logical for the stated purpose, which is to generate *ranking of food-hazard pairs*. The interactive web-based implementation of iRISK is user-friendly and easy to navigate.

RESPONSE: FDA thanks this reviewer for their comments.

Short-Term Action Items:

[**COMMENT G-1-4**] Some of the inputs are very conservative and not necessarily an accurate reflection of estimated risk. For example, in the case of aflatoxin, the cancer risk quoted and used in the model is for aflatoxins from all sources of aflatoxins—it is expected to be that the actual contribution of aflatoxins in tortilla chips would be a very small portion of the total exposure to aflatoxins.

RESPONSE: As noted in the peer review workbook the examples provided were intended to function only as illustrations of the use of the tool and so the inputs listed may not necessarily provide faithful representations of the risk. We agree that the contribution of tortilla chips to exposure may be very small. The choice of tortilla chips is arbitrary and not meant to suggest that this food is an important source of risk.

[**COMMENT G-1-5**] A word of caution is suggested in using different sources for information—i.e., U.S. consumption data, levels of contaminant in non-U.S. markets.

RESPONSE: The value of the examples provided was in illustrative capacity rather than an estimation of the risk in a specific context. Consistency among sources of data is preferable and, where data from different sources are used, this should be documented in the risk scenario. The reviewer was able to detect the possible issue by considering the

notes entered by the simulated user in this example, which demonstrates the potential transparency of the tool, and allows for such caution to be employed.

[**COMMENT G-1-6**] However, this reviewer has been unable to validate the outputs of this model. First, although the inputs were well-documented, the reviewer was unable to take the final output and calculate back through the system to ensure that this will match the initial inputs (presumably this was done by the model developers).

RESPONSE: The FDA-iRISK tool builds a model (behind the scenes) in the software Analytica Decision Engine (Lumina Decision Systems, Los Gatos, CA), which provides a visual characterization of the model, as well as all intermediate calculations, thereby providing for a detailed audit trail behind the calculations. These calculations have been reviewed and tested by the model developers.

[**COMMENT G-1-7**] Other issues that this reviewer can see: most toxicological data for chemicals are incomplete, inconclusive, often contradictory, and where available, are based on extrapolation from animal models;

RESPONSE: While we agree with the reviewer's general characterization of the challenges in applying toxicological evidence, the necessity of generating estimates of risks to humans requires that we proceed with what is available and acknowledge the challenges. This is facilitated by careful recording of assumptions, and through generation of alternate scenarios which represent different interpretations of the evidence.

[**COMMENT G-1-8**] Other issues that this reviewer can see: …it is not possible to relate the estimated number of total illnesses to actual health metrics from a given population, as this information is not available (estimates are available at best);

RESPONSE: We agree with the concern that there are few instances where there is a known food-specific estimate of the number of illnesses associated with chemical hazards, with which one could compare the results of FDA-iRISK. Accordingly, the capacity to predict and rank potential foodborne sources of illness due to chemical hazards using tools such as FDA-iRISK is important to inform risk-based decisions to ensure food safety. Even where estimates are available, the level of agreement between the FDA-iRISK results and an external estimate would be primarily driven by the assumptions made by the user rather than the calculations conducted by FDA-iRISK.

[**COMMENT G-1-9**] Other issues that this reviewer can see: …the difficulty in linking illnesses from chronic exposure to a specific hazard-food combination or even a specific hazard in most cases (in the presence of other potential causes or sources of disease);

RESPONSE: FDA-iRISK is a bottom-up method of predicting the risk resulting from exposure to a food-borne hazard, and this applies to both acute and chronic exposures. There are known challenges with evaluating chronic chemical exposures, as well as with developing dose-response models for those exposures. The FDA-iRISK model does not

create this challenge, but is intended to facilitate the ability to express what is known and unknown about the level of risk associated with exposure to a chemical hazard in food.

[**COMMENT G-1-10**] Other issues that this reviewer can see: …quantification of chronic risk for low levels of contaminants and low probability of health effects;

RESPONSE: As noted in the response to Comment G-1-9, the challenges of low-dose extrapolation are well-known and recurring issues. The FDA-iRISK tool provides a wide variety of dose-response models for flexibility in addressing how risk may be predicted from chronic, low doses of contaminants. The user can choose an appropriate dose-response model, including the choice of whether to employ a low-dose linear or threshold-based response, among other options.

[**COMMENT G-1-11**] Other issues that this reviewer can see: …differences between individuals in their susceptibility to chemical or microbial hazards;

RESPONSE: FDA-iRISK allows for the characterization of distinct population groups whose risks can be predicted separately (both with respect to the probability of illness and the severity of the outcomes). These can also be combined in a composite scenario at the population level, taking into account the relative size of the sensitive group.

In addition to a categorical description of susceptible populations (e.g., addressing known, identifiable groups), inter-individual differences in sensitivity can be represented in the parameters (and therefore the shape) of the dose-response model. Options exist for both microbial and chemical hazards. For example, different parameter "*r*" values can be used for the exponential dose-response relationship for the "perinatal", "intermediate-aged", and "adults 60+" subgroups having different susceptibility to *L. monocytogenes* infection (Chen et al. 2013). Similarly, known or suspected changes in susceptibility to chemical hazards can be implemented by defining alternate dose-response curves for different subpopulations, for example, to reflect a higher probability of liver cancer for people with Hepatitis B given exposure to the mycotoxin aflatoxin B_1 (JECFA, 2001). These dose-response curves are then applied to the specific subpopulations within FDA-iRISK.

In addition to the ability to separately address the probability of illness among different subpopulations, FDA-iRISK allows for the development and application of specific burden of disease (e.g. DALY) estimates where the individual susceptibility is related to the probability of more severe outcomes of any illness.

[**COMMENT G-1-12**] Other issues that this reviewer can see: …and no efficient means of demonstrating that the outputs of this model are similar to other model outputs or risk assessments available in the literature, and comparing the DALYs to maximum limits/levels (enacted with safety factors and should lead to no unacceptable health concerns).

RESPONSE: As part of the development of FDA-iRISK, an existing FDA risk assessment for inorganic arsenic (Carrington et al. 2013) was replicated (with some simplifications) within FDA-iRISK, which predicted comparable number of cancer cases (median

estimate). As discussed in previous comments, there are few instances where predicted or observed health effects from chemical exposure are available for comparison to results generated by FDA-iRISK. This issue is common to all risk assessment tools that would require some sort of external validation.

[**COMMENT G-1-13**] Another issue is that there are no clear means to deal with metabolism (degree of elimination, inactivation of the chemical by the body, conversion to metabolites of toxicity, which may differ from the parent compound).

RESPONSE: The reviewer is correct that FDA-iRISK does not explicitly address the metabolism issues. However, depending on the nature of the evidence base chosen by the user to develop the dose-response model, these aspects of predicting the toxic response may be taken into account. FDA-iRISK v1.0 only provides for dose-response relationships with external (ingested) dose; it does not have the capacity to model tissue-level or other internal dose metrics. To the extent that metabolism is important, this would be subsumed within the dose-response relationship whether derived from external doses from human studies or animal studies. To the extent that there is a known differential impact related to metabolism (e.g. variation in bioavailability given food processing or preparation as in Laparra et al. 2005), this could be represented by a reduction in the effective concentration (and thereby the effective dose) through a decrease step in the process model.

[**COMMENT G-1-14**] The reviewer acknowledges that with acute chemical hazards there is a measurable level of a hazard in the patient, health effects from contaminants in the food source, and this can be correlated to incidence of disease. However, the vast majority of chemical hazards are chronic risks for which such clear correlations cannot be made.

RESPONSE: FDA recognizes that attribution of risk to specific chemical hazards in specific foods based on observational evidence (e.g., epidemiological studies) is extremely challenging. This underscores the need to generate predictive models of risk using a tool like FDA-iRISK in order to identify exposures of potential concern and evaluate the effectiveness of potential mitigation strategies to inform the allocation of resources.

[**COMMENT G-1-15**] Chemical hazards, microbial hazards, and microbial toxins can exhibit both chronic and acute effects depending on concentration. It is not clear how to address this in the given model without running entirely different scenarios.

RESPONSE: The reviewer is correct that the user is required to characterize acute exposures and chronic exposures separately. The risks from the acute exposure scenario and the chronic exposure scenario can be grouped (i.e., the risks summed) by the user when generating the risk ranking report. This result generates an overall risk estimate with a common denominator (e.g., cases or DALYs per year, with chronic risk annualized by dividing by the duration of exposure). The grouped scenario is reported as such in the output report, providing a single view of risk from two types of exposure. We believe this format provides the greatest flexibility.

For chronic effects of exposures that are considered to be chronic sequelae of an original

infection, or chronic conditions resulting from an acute exposure event, these effects can be directly incorporated in the health template (i.e., DALY per case), which takes into account their frequency of occurrence, the severity of the effect, and the duration of the effect. The predicted health burden will be the sum of the effects of both acute and chronic health outcomes from the acute exposure.

[**COMMENT G-1-16**] One of the fundamental issues this reviewer had was to understand the concept of burden of disease and DALY scores across a population when much of the exposure and risk assessment information focuses on individuals. It is presumed that the higher the DALY score, the greater the risk. Because of the description of this metric as "disability-adjusted life years," the overwhelming response is to attempt to convert this to a metric for a person and this is not feasible. There does not appear to be a finite limit as to how small or how large this number can be. This makes it difficult for this reviewer to provide context as to what is a low risk and what is a high risk. It would be helpful if the developers included a blurb on "typical" or specific cases of DALY scores to help with context. Another idea is to rename this metric or convert it to a dimensionless number that would describe the overall health impacts.

RESPONSE: FDA recognizes that some users will not necessarily be familiar with the concept of DALY and may require some support in interpreting the results. The DALY value for an individual health outcome ranges from 0 to approximately 80 (with 0 representing no harm, and 80 representing a complete loss of life at birth). This measure, though new to many in food risk assessment, has been used extensively for decades. An example is the use of DALY by the World Health Organization in developing guidelines for safe use of wastewater in agriculture[1]. For a population, the burden is simply the sum of individual DALY values weighted according to how often individuals experience each type of health outcome. Due to the increasing use of DALYs and similar measures which explicitly acknowledge the considerable variations in probability, severity and duration of health effects (Havelaar and Melse 2003, RIVM 2006, Howard et al. 2007, Murray and Lopez 1997, Murray et al. 2012), we find this type of measure (and similar ones such as Quality-Adjusted Life Years) preferable to a dimensionless number. We plan to continue reviewing the strengths and weaknesses of the application of health-adjusted life years, e.g., as described in recommendations by the Institute of Medicine (IOM 2006). FDA will consider enhancing documentation with regards to DALYs in future versions of FDA-iRISK.

[**COMMENT G-1-18**] Also, an assumption is made that a hazard is homogenously distributed in the food. This is not a reasonable assumption for either microbial hazards or microbial toxins, which tend to occur in pockets. The food should be homogenized prior to analysis.

RESPONSE: The FDA-iRISK tool allows for a user-specified level of variation in the concentration of organisms *between units* of food (e.g., between-unit variability in concentration). For example, if the user has specified that the unit of food is equivalent to the batch of milk collected for cheese-making from a single herd, then the user can specify that some batches of milk will have no contamination of a pathogen (e.g. *Listeria monocytogenes*), whereas contaminated batches of milk can have more or less

[1] http://www.who.int/water_sanitation_health/wastewater/gsuww/en/

contamination, as described in a joint FDA/Health Canada draft risk assessment (FDA/HC 2012). The homogeneity assumption is limited to homogeneity within each unit of food while allowing different units of food to have different concentrations. This assumption affects calculations where the unit is later subdivided such that subunits of the food have an equal likelihood of contamination in proportion to their size, according to the Poisson distribution.

[**COMMENT G-1-20**] Although the user manual does indicate that the reviewer can enter a single number or a range of numbers, it is not always apparent how to input the range.

RESPONSE: A range can be entered by using the "Distribution" drop-down menu and selecting the appropriate choice: e.g. "Uniform". The appropriate input fields (in this case "Minimum" and "Maximum") then appear to accept the user's data and assumptions. We see that this issue can be addressed through training.

[**COMMENT G-1-21**] This reviewer would like to see a particular validation exercise for acute hazards—select a few cases where there is a well-documented number of illnesses and levels of a given contaminant (chemical or microbial) in the associated foods, run the model using these conditions, and demonstrate that the model outputs correlate with the actual number of illnesses and/or deaths reported. From there, proceed with the ranking of these acute hazards and verify the findings— against other risk assessments, other models used in risk assessment, or scientific literature.

RESPONSE: It would be valuable to obtain data from an outbreak in which the concentration and prevalence in the food at consumption, the total number exposed, and the dose-response model are known in order to implement these data in an FDA-iRISK scenario and compare the predicted risk with real-world results. For example, it would be possible to develop validation scenarios for acute outbreaks with known prevalence and concentration of contamination, e.g., as was done by Danyluk and Schaffner (2011) to simulate the *E. coli* O157:H7 in spinach 2006 outbreak.

[**COMMENT G-1-22**] In this reviewer's opinion, it has not been fully demonstrated that the tool has been sufficiently developed to meet the two objectives as listed.

RESPONSE: FDA is continuing to develop and refine the FDA-iRISK tool and is conducting a series of case studies which demonstrate its capacity, in parallel to the peer review process.

[**COMMENT G-2-3**] My main concern is the modelling of the chronic chemical hazards, which is quite different from acute (microbial) risks. The LADD concept is not perfectly clear to me: If the means used for its calculation (Section 4.2) are means over time, this is okay. If, however, they are means over the population (in which people experience varying exposure due to differences in consumption), the risk assessment may be misleading. I do not understand which means are taken, and how the different distributions are applied/aggregated to a mean. This is essential and should be explained in more detail

RESPONSE: The LADD is calculated on a per-consumer basis, and represents the average daily dose over an individual person's lifetime. The dose in mg/kg body weight at each life stage is calculated, and these values are weighted by the proportion of the lifespan spent in each life stage. The resulting LADD belongs to a distribution of LADDs representing the various chronic exposures of the population of consumers. We agree that averaging across individuals is inappropriate. There is no averaging of exposure across individuals in FDA-iRISK. The Technical Documentation has been revised to provide details of the calculation and an illustration of the flow of calculations and we plan to make the revised document available.

[**COMMENT G-2-4**] … I indicated that the document is missing: 1) An explanation why the tool is considered to be specifically suited for risk ranking and not for other purposes…

RESPONSE: Where there are unavoidable weaknesses in the inputs (e.g. the dose-response model used for chronic chemical exposures) FDA-iRISK offers the benefit of a consistent and transparent system for predicting the risk. This consistency supports ranking among risks estimated using the same system, but does not compensate for poor data such that the result can be considered an accurate estimation of the risk. In addition to risk ranking, we believe the tool can be used for other purposes. With the built-in model structure and features, FDA-iRISK allows users to conduct fully probabilistic risk assessments relatively rapidly and efficiently. In developing FDA-iRISK, we have tried to provide a tool that automates the often time- and labor-intensive process of developing mathematical models to simulate risks and interventions in food production chains, giving regulatory and industry decision-makers a systematic way of comparing risks in the food supply and predicting best solutions.

[**COMMENT G-2-5**] …2) References to previous work on which the concepts applied in iRISK seem to be built. … and the ILSI report on Microbial distributions (ILSI 2010).

RESPONSE: The Technical Documentation has been revised to provide references to material employing concepts similar to those applied in FDA-iRISK, including those identified by the reviewer and we plan to make the revised document available.

[**COMMENT G-4-3**] The 2010 Institute of Medicine & National Research Council Report *Enhancing Food Safety: The Role of the Food and Drug Administration* lists FDA-iRISK as a "Semiquantitative Food Safety Risk-Ranking Method" (Chapter 3, Adopting a Risk-Based Decision-Making Approach to Food Safety; Table 3-1, page 88). This description is probably more accurate than that of the Technical Fact Sheet, above, even when recent refinements and additions to iRISK are taken into account. Considered in the context of semiquantitative risk-ranking methods, iRISK is a valuable tool, with the potential of becoming an excellent tool if its development continues to be supported appropriately.

RESPONSE: We believe the description in the Technical Fact Sheet is accurate in stating that FDA-iRISK is a fully quantitative tool. Using "semi-quantitative" would not adequately capture its capacity. FDA-iRISK allows users to conduct fully quantitative, fully probabilistic model and to generate risk estimate as the DALY value as well as the

number of cases, in the same way that risk is estimated from "probability x consequence" as in other FDA quantitative risk assessments (e.g., FDA/HC 2012, Carrington et al. 2013).

[**COMMENT G-4-5**] The *caveat* associated with this prospect (of very easy and wide access and usage) of FDA-iRISK is the increased potential of its misuse, with subsequent associated misinterpretation of results. While model descriptions warn that "to populate the dose-response model with their data, users must know which of the model options offered by FDA-iRISK (e.g., Beta-Poisson versus exponential)," this is only one example of the multidisciplinary expertise that is needed to properly use the model; in fact, the dose-response modeling component of iRISK offers a far more complete set of options than the exposure modeling component, which is more "open" to (potentially inappropriate) user selections of inputs and parameters.

RESPONSE: As far as possible, FDA-iRISK endeavors to provide the user with sufficient flexibility to represent the risk posed by foodborne hazards. As with any flexible tool, the user is not constrained in characterizing foods and hazards. The primary contribution of FDA-iRISK is to appropriately combine (structurally and mathematically) the user's assumptions into an estimate of risk, assuming that the user's inputs are valid. This removes an error-prone component of the risk assessment process. The user is provided with ample opportunity to document the basis of their assessment, and this information is available to be included in any output results. Both the exposure modeling and dose-response components of FDA-iRISK require a knowledgeable user to generate appropriate results. We are unable to predict which of these components are more prone to inappropriate use at this time.

[**COMMENT G-4-9**] First, the expected range of applicability of iRISK (and its "location" in the universe of currently available models and databases) needs to be defined, in conjunction with the expected attributes (resolution, accuracy, reliability, etc.) of estimates/outcomes of the model.

RESPONSE: In the early stage of development, FDA commissioned a study in 2008 to evaluate available food safety risk ranking and prioritization models. The study evaluated the Food/Hazard Risk Registry (FHRR) developed by a panel convened by the Institute of Food Technologists, Risk Ranger, the Food Sector Risk Ranking and Prioritization Model, the Foodborne Illness Risk Ranking Model, and the Food Safety Universe Database. Based on the evaluation of the scope, strengths and limitations of the available models then, FDA selected the FHRR as the prototype for further development and peer review, leading to FDA-iRISK 1.0 made public in 2012. We recognize that it would be useful to identify the location of FDA-iRISK within the universe of tools available. At this stage, this is challenging due to the increasing number and complexity of available tools, including keeping track of changes to these other tools. In any case, we believe that it would be more appropriate for a third-party to independently characterize the universe of available tools.

[**COMMENT G-5-3**] Nevertheless, the following considerations for iRISK are noted: FDA-iRISK is simply a modeling platform and users are required to supply all the data and information necessary to conduct an assessment. As such, the validity of any results derived from FDA-iRISK will be contingent upon the user's input information. This should be made clear in any presentation of FDA- iRISK to avoid the perception that risk assessment results derived from using FDA-iRISK has FDA's endorsement.

> **RESPONSE:** FDA agrees with the reviewer. The current version contains a disclaimer appearing during user login and in the output reports. The disclaimer language will be reviewed and updated as appropriate.

[**COMMENT G-5-5**]…Since iRISK was initially developed based on microbial risk assessment, terminology and varying degrees of complexity (in the process module) may not be familiar to a chemical risk assessor. As such, a glossary of terms to orient a chemical risk assessor to the terminology used in iRISK would be helpful.

> RESPONSE: FDA-iRISK has been developed to address both microbial and chemical hazards from the onset of the project. To the greatest extent, the FDA-iRISK tool uses generic terminology except where hazard-specific language is required. The only area where the terminology is not generic to food risk assessment is in the process-oriented components of food production. These may have more familiarity to those attempting microbial risk assessment due to the familiarity with considering processing effects (e.g., inactivation during cooking and growth during storage) on microbial hazards. The User's Guide describes these components of a process model, and separately describes how they relate to microbial and chemical hazards. We plan to add a glossary of terms to the user interface in future versions.

[COMMENT G-5-6] Also, examples with explicit calculations are needed in the Technical Documentation to help readers better understand how the models are actually implemented and how the input from the various components of iRISK is integrated (see more detailed comments on this below).

> **RESPONSE:** The Technical Documentation for FDA-iRISK has been substantially updated as part of the response to this peer review, including some example calculations for transparency and to improve understanding by readers, and references for functions and equations. We plan to make the revised document available to users in the near future. We also plan to add more examples in future revisions.

[**COMMENT G-5-7**] The Workbook for Peer Reviewers (Implementing Chemical Risk Scenarios in iRISK)— a guide on operating iRISK—starts with the hazard module, then onto consumption and process aspects, while the Technical Documentation starts with the "process" aspect of iRISK. This is very confusing. Assuming the Workbook for Peer Reviewers is a form of a user's guide that guides the users through each step of an assessment, the Technical Documentation should be revised to have the same flow/sequence of information as the User's guide. This will make it easier for readers to follow the calculation at each step of the web-based tool.

RESPONSE: The Technical Documentation has been extensively revised, including the order in which concepts are presented. Some level of compatibility between these documents has been sought, though this is inherently limited by the fact that the two documents have entirely different purposes (step-by-step instruction versus understanding the mathematical basis of the tool). FDA plans to make the revised document available to users.

Longer-Term Action Items:

[**COMMENT G-1-17**] It would be helpful if the model could prompt the user to search for tolerable daily intakes, NOAELs, or regulatory limits which may assist in determining dose-response.

RESPONSE: As the use of FDA-iRISK is independent of any regulatory requirements, it is currently outside of the scope of the tool to provide guidance that would link to TDI, NOAELs, or regulatory limits. We have made the tool publicly available, with potentially multi-jurisdictional and international users. As such, it would be difficult to identify specific regulatory limits without limiting, or suggesting a limitation in, the use of FDA-iRISK across a variety of jurisdictions.

[**COMMENT G-1-19**] This reviewer would like the option to link to specific Microsoft Office based products such as Excel that contain information that supports prevalence or concentration data being used in the model.

RESPONSE: FDA is considering the possibility of providing selected outputs in a Microsoft Excel or Microsoft Word format, to facilitate the ease with which a user may integrate the outputs into other work processes. We will evaluate and as appropriate address this issue, taking into consideration the challenge associated with allowing direct integration of inputs from an Excel or other format due to the variety of ways in which external data may be stored, and diversity in versions of other tools to which to connect FDA-iRISK.

[**COMMENT G-2-6**] … I am unsure that you showed that iRISK is a powerful tool for risk ranking. You show it can assess DALYs for various combinations of food and pathogens, and for all kind of production processes, but you don't show how it performs in risk ranking. A crucial question is: how large should a difference in risks (DALYs) be to conclude that one ranks significantly higher than another? This question is not addressed. Yet it is crucial if the risk ranking results are to be used for decision making.

RESPONSE: At this point in time, FDA-iRISK has not been extensively used in risk ranking, while it is increasingly used for individual risk assessments. We continue to develop a library of risk scenarios to generate risk ranking results. As more experience is gained, it will help us address this issue. The question of how large a difference in DALYs is required to qualify as "ranking significantly higher" is dependent on a great

many factors that are context dependent. The addition of new features for sensitivity analysis and uncertainty analysis (under consideration) will let users determine how sensitive risk estimates are to key assumptions. This will allow the user to judge whether the risks associated with one or more scenarios should be considered "significantly" different in light of the uncertainty in estimated input.

[**COMMENT G-3-2**] Decision Framework or Guidance: In the dose-response section, reference is made to EPA's Benchmark Dose Software, which made me think about whether some of the BMDS documentation might be useful as models for iRISK. One very important piece of BMDS documentation and training is a step-wise plan for modeling. It includes the basic process to follow and also guidance on important decisions that are made during the process.

RESPONSE: We thank the reviewer for this suggestion and agree with the premise that the USEPA's BMDS documentation has a number of user-friendly qualities as described. While we recognize the value of detailed instructions, the primary focus of FDA-iRISK is not intended to educate users in step-by-step decisions involved in deriving input values and other choices. The User's Guide for FDA-iRISK, and the Tutorial, follow a step-by-step approach, though the user is ultimately free to develop the seven components of each model in any order as the tool supports both approaches.

[**COMMENT G-3-3**] If iRISK will be used by FDA stakeholders (food industry groups or consumer groups), it may be necessary to develop training on both the nuts-and-bolts of using the tool and, more importantly, guidance on how to interpret results – or to articulate FDA's approach to interpreting results.

Some considerations for developing guidance/best practice include describing:

- What types of source data are preferred by FDA for all user inputs?
- What level of documentation and referencing does FDA expect, if an external party is submitting an iRISK report on a topic of concern?
- What are minimum expectations for scenario analysis to address important uncertainties?

RESPONSE: FDA concurs with the reviewer that more training would facilitate broader use of FDA-iRISK by stakeholders. Concurrent with the launch of FDA-iRISK 1.0 in 2012, FDA provided a webinar to all stakeholders, hosted by the Joint Institute for Food Safety and Applied Nutrition (JIFSAN). Subsequent to the launch, FDA provided a 2-day training course, through Risk Sciences International (RSI), for risk assessors and technical staff from Federal agencies in the U.S. and Canada. We developed a User Guide and a Quick Start Guide to accompany the Technical Documentation 1.0, and plan to update and provide revisions of these documents for users. Whether or not FDA may provide further training will depend on availability of resources. With regard to requirements for data quality, risk scenarios developed in FDA-iRISK would not differ from other food safety risk assessments, and guidance on data quality is available, for example, from the Office of Management and Budget (OMB) "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies"[2]. The purpose of FDA-iRISK is to provide an appropriate database and computational infrastructure to support a

[2] The OMB guidance is available at http://www.whitehouse.gov/omb/fedreg_reproducible.

majority of the types of calculations typically required in risk assessments applied to food safety. FDA has made the tool available to stakeholders so that users can enter their own data, generate results and make their own interpretation. FDA plans to further develop the tool, taking into consideration recommendations from the reviewers, for example by including the capacity for uncertainty characterization. A key design principle behind FDA-iRISK is that the combination of the user's technical knowledge and the reliability associated with the computational infrastructure should ensure higher quality and more productive risk assessment activity.

[**COMMENT G-3-4**] Peer Review Materials: Clarity/Ease of Use: It can be difficult to navigate the workbook because as you progress to the 2nd and 3rd scenarios (histamine and ammonia) you are referred back to the aflatoxin scenario for step-by-step instructions. If the existing workbook is used for other training purposes, it might be easier to use (and facilitate better success for trainees) if all instructions are presented for each scenario.

RESPONSE: The balance between repeating and referring back within the documentation will be revisited. Documentation for FDA-iRISK is continually updated as the tool evolves, and this concern will be taken into account in the next revision of these documents.

[**COMMENT G-4-2**] It should be recognized, however, that currently iRISK is still in an early phase of development. It will require extensive enhancements in order to actually "fit," sometime in the future, if that is actually the objective of its development. The ambitious description provided in the first sentence of the Technical Fact Sheet[3] titled "A Closer Look at FDA-iRISK," states that iRISK "is available to the public, to enable users to relatively rapidly conduct fully quantitative, fully probabilistic risk assessments of food-safety hazards."

In fact, "fully quantitative, fully probabilistic risk assessments" are challenging multidisciplinary enterprises that, in the case of food-safety hazards, require resources and expertise in food science and engineering, exposure science, human behavior, consumer demographics, physiological dosimetry, human toxicology, public health, statistical methods of uncertainty and sensitivity analysis, etc. Individual human expertise needs to be supplemented by comprehensive databases and well-tested mathematical models, both mechanistic and empirical, from each of these fields in order to collaboratively produce *scientifically defensible* quantitative probabilistic risk assessments.

RESPONSE: It is unclear from the reviewer's comment what specific enhancements of FDA-iRISK would be required to have it "fit". It appears that most of what the reviewer seems to be suggesting for enhancements is external to FDA-iRISK (sufficient knowledge in various disciplines, mechanistic models, and better data). The FDA-iRISK tool is quantitative, and is probabilistic. We believe that the quoted text from the Technical Fact Sheet is reflective of the current capacity of FDA-iRISK, even though

[3] The Technical Fact Sheet is available at http://www.fda.gov/downloads/Food/ScienceResearch/ResearchAreas/RiskAssessmentSafetyAssessment/UCM316706.pdf

more efforts are underway to add more features to the tool to enhance its capacity. We believe it is important to separate challenges in the field of risk assessment from the adequacy of the underlying structure and built-in features of FDA-iRISK as a food safety modeling tool. FDA has conducted case studies for microbial hazards using the tool (Chen et al. 2013) and continues our efforts to develop more case studies, in particular for chemical hazards. We plan to use comments from this peer review to help guide further development and validation of the tool.

[**COMMENT G-4-8**] However, in order for this potential to be fully materialized, considerable effort needs to be placed towards developing information and guidance for its proper usage.

RESPONSE: We agree with the suggestion and recognize the needs identified by the reviewer. Depending on the data available to each user or organization hoping to use FDA-iRISK, and depending on the intended purpose of the resulting estimates, the required information and guidance can vary. We will take this comment under consideration and address the needs as appropriate moving forward.

[**COMMENT G-4-10**] Second, scientifically defensible "default" and representative estimates for various parameters and distributions of exposure-relevant factors need to be developed, at least for the U.S. population for which extensive databases (such as NHANES, CSFII, CHAD, etc.) are available, while many summaries of factors are directly available in the two *USEPA Exposure Factor Handbooks*.

RESPONSE: FDA-iRISK is intended for international use as well as for use in the United States. As such, no assumption is made as to the appropriateness of any specific source of exposure or consumption data. The FDA-iRISK tool is available through the JIFSAN-hosted site (www.foodrisk.org), which provides multiple sources of (or links to) information of the type identified by the reviewer. This resource can be continually updated independently of FDA-iRISK for multiple uses, while being convenient to users of FDA-iRISK. In addition, the sharing capacity in FDA-iRISK enables users to share data, including exposure data entered into a risk scenario, e.g., process model and consumption model data and related notes.

[**COMMENT G-4-11**] Third, detailed Technical Guidance, utilizing the content of publicly available works from U.S. Agencies, as well as from WHO and from European Agencies (see references at the end of the present review), should be developed and linked on-line with model features, to facilitate proper application of future versions of FDA-iRISK.

RESPONSE: As indicated above, the primary focus of FDA-iRISK is not intended to educate users in step-by-step decisions involved in deriving input values and other choices. We will take into consideration this suggestion in future revisions of the FDA-iRISK User's Guide, the Tutorial and on-line instructions linked to model features as appropriate. Other sources of risk assessment guidance are available, for example, through the JIFSAN-hosted site (www.foodrisk.org), which provides multiple sources (or links to) of information of the type identified by the reviewer.

[**COMMENT G-5-4**] Additionally, if there is any plan to create an inventory of data input by users of FDA-iRISK at large, the peer-review status of such a data inventory will need to be clearly detailed and documented.

> **RESPONSE:** FDA will evaluate feasibility of creating an inventory of data and consider this suggestion in future development of the tool. We agree with the reviewer that review of data (including peer review) is important when using any data to develop risk scenarios. Meanwhile users are encouraged to document the sources and confidence associated with all inputs and assumptions. User input is only shared by users with specific people with whom they choose to share.

CHARGE QUESTION 1: COMMENTS AND RESPONSES

CHARGE QUESTION 1: *The FDA-iRISK model estimates risk and generates ranking of food-hazard pairs through a pre-determined model structure consisting of seven elements requiring user-supplied data and information: the food, the hazard, the population of consumers, process module describing the introduction and fate of the hazard up to the point of consumption, consumption patterns, dose-response curves, burden of disease metric. Is the overall modeling approach fundamentally sound for the risk ranking purpose and scope? If not, what problems exist and how should they be addressed?*

Noted Strengths:

[**COMMENT 1-2-1**] The overall modeling approach is based on the risk assessment paradigm, built by combining hazard identification (the hazard), exposure assessment (the food, the population of consumers, and the process module and consumption patterns), hazard characterization (the dose-response), and risk characterization (burden of disease). It is well suited to compare different risks.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 1-3-1**] I find the iRISK modeling approach technically sound and relatively easy to use. This will be a very useful tool for food safety risk assessment.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 1-5-1**] The FDA-iRISK model generates ranking of food-hazard pairs via a pre-determined model structure consisting of seven components: food, hazard, population of consumers, process module describing the introduction and fate of the hazard up to the point of consumption, consumption patterns, dose-response curves, and burden of disease metric. This reviewer has some specific comments on various aspect of the iRISK model (see below), but, in general, the overall model construction is logical for the stated purpose of iRISK, which is to generate *ranking of food-hazard pairs*.

RESPONSE: FDA thanks this reviewer for their comment.

Short-Term Action Items:

[**COMMENT 1-1-1**] As mentioned, disease burden is very difficult for this reviewer to use in the context of risk ranking. A particular numerical score could be associated with a short-lived disease that hits many people and a disease that occurs less frequently but is lethal in most cases.

RESPONSE: The DALY metric is designed to address exactly this dichotomy, since it is intended to represent the impact of disparate illnesses at a population level. The implication is that 100 DALYs represents the same burden on a population whether the cause is many mild illnesses or a few serious illnesses (or deaths).

[**COMMENT 1-1-3**] The model does not readily take into account that most microbial contamination is associated with acute, non-lethal illnesses of short duration, that microbial contamination can be zero, and that the bacterial level can be clearly detected in the human body or in the food.

> **RESPONSE:** We respectfully disagree with this comment from the reviewer. FDA-iRISK does provide a means for modeling acute effects from microbial contamination in food. This can be done through the input of a dose-response model representing illness endpoints such as salmonellosis from *Salmonella* contamination in peanut butter (see case study in Chen et al. 2013) which is acute in comparison to chronic illness caused by carcinogens such as inorganic arsenic in apple juice (Carrington et al. 2013). Furthermore, FDA-iRISK applies health metrics (e.g. DALYs or Cost per Illness) which incorporate the relative frequency, severity and duration of various health outcomes caused by illnesses from microbial contamination. FDA-iRISK allows the user to specify prevalence values less than 1 which results in a fraction of all servings having zero contamination. As well, process types such as decrease can reduce the fraction of servings that are contaminated.

[**COMMENT 1-1-4**] For chemicals, most of the hazards are chronic and often lethal; there is no true zero, rather there are levels below and above the limit of detection of the method; and the presence in the human body may not be easily detectable (even if it can be bio-monitored, it is unlikely that one could correlate these levels with the development of a particular disease in the presence of other confounding factors such as other sources for the disease state).

> **RESPONSE:** While we agree with the reviewer's general characterization of the challenges in applying toxicological evidence, the necessity of generating estimates of risks to humans requires that we proceed with what is available and acknowledge limitations in data and uncertainties. Furthermore, whether or not there is true zero for certain chemicals in foods would need further evaluation, depending on the nature of the chemical in the environment and whether or not it's used for certain crops, e.g., toxic elements vs. pesticides. Please see the responses to Comment G-1-7 and Comment G-1-8 addressing similar concerns.

[**COMMENT 1-1-6**] The model does not actually consider food—it considers particular food commodities. This is important in distinguishing this risk ranking from a full risk assessment that would consider all foods in which the hazard could be found and all forms of the food in question. In the case of aflatoxin, this would mean consideration of fruits, corn and nuts (dried/frozen/fresh fruits/juice/wine from warm regions, nuts/nut butters, raw corn, canned corn, corn-based breakfast and infant cereals, corn tacos/tortillas/tortilla chips, corn starch, corn syrup and foods sweetened with corn syrup, etc.).

> **RESPONSE:** We agree with the reviewer that multi-food risk assessment for chronic chemical hazards is not available in version 1.0 of FDA-iRISK. This feature is currently under development and we plan to make it available in a future release.

[**COMMENT 1-2-2**] I do, however, think that risk assessment should not be the only consideration for risk ranking. Epidemiological data should be considered as well; if iRISK ranks a risk high, but no cases are known in the population, this finding should be a concern. And the other way round; if epidemiology points at a risk and the risk assessment doesn't. Such a finding would (and should) lead to interesting scientific discussion. I don't think this aspect can easily be added to iRISK, and I don't think it should. It is just a limitation that follows from the approach.

> **RESPONSE:** We recognize that risk ranking may be carried out by using risk assessment (such as by using FDA-iRISK) or another approach such as an epidemiological-based method that involves the analysis of public health surveillance data (Batz et al. 2012). If for a food-hazard pair the FDA-iRISK tool consistently provides estimates that are at a variance with epidemiological data, the user should re-assess the inputs used in order to identify what is causing the different results and whether appropriate data and valid assumptions have been used. Since there are strengths and limitations in different approaches, results from FDA-iRISK using appropriate data and valid assumptions may provide new insight into disease burden given that there is recognized uncertainty in illness estimates using epidemiological data (Scallan et al. 2011). FDA-iRISK generates predictions of foodborne risks in support of risk ranking exercises, and the results are expected to be considered by risk managers in concert with other considerations, among which might be epidemiological data.

[**COMMENT 1-4-1**] The *overall modeling approach/framework of iRISK is fundamentally sound;* however, it would be very useful—or even essential—to define the above mentioned "risk ranking purpose and scope" in more precise terms.

> **RESPONSE:** FDA will take this suggestion into consideration in efforts to further refine the risk ranking purpose and scope of FDA-iRISK. We expect the definition will continue to be refined and evolve as the FDA-iRISK tool is further developed and used in more case studies as well as in FDA collaboration with other organizations. Our current thinking on FDA-iRISK can be found in a recent publication (Chen et al. 2013) and a publically available Fact Sheet[4].

[**COMMENT 1-4-2**] Indeed, as opposed to most environmental/health/risk-related models currently available, iRISK offers a wide range of options (involving assumptions, parameter selections, input selections, etc.) completely "open" to the user, with only minimal amount of technical/scientific guidance and minimal restrictions in model and scenario development. [It would probably be accurate to state that iRISK is a structured—but flexible—modeling framework or system, allowing the development of multiple (and alternative) case-specific models.] This can create potentially serious problems, especially if a user does not have extensive expertise relevant to all of the "seven elements" listed above (food, hazard, population of consumers, process module, consumption patterns, dose-response models, burden of disease metric).

> **RESPONSE:** Please see the response to Comment G-4-5.

[4] Available at http://www.fda.gov/downloads/Food/FoodScienceResearch/UCM316705.pdf.

Longer-Term Action Items:

[**COMMENT 1-1-2**] The model cannot currently account for hazards that have both acute and chronic health effects. The disease burden, at least to the understanding of this reviewer, does not allow for a mechanism to consider endocrine disruption and health effects on the developing fetus, defects resulting in miscarriages or long-term health issues.

> **RESPONSE:** The burden of a hazard having both acute and chronic health effects can be estimated by creating separate scenarios for each of the two forms of exposure and aggregating the resulting risk. Fetal effects can be modeled by considering exposure to the mother, and defining the illness (health endpoints) as experienced by the child. For example a stillbirth would have a duration equal to Life Expectancy at Birth, even though the mother consumed the food.

[**COMMENT 1-1-5**] The model does not consider the impact of regulations and testing activity (either initiated or required prior to import). The initiation, repeal or alteration of regulations and/or testing activity may have an impact on the prevalence and the levels of hazards observed in foods.

> **RESPONSE:** A process type to reduce the prevalence by testing and removing contaminated product (i.e. representing sampling) is under consideration as a new feature for a future version of the tool.

[**COMMENT 1-4-3**] Clearly, the current "levels" of applicability of iRISK (presumably ranging from "screening" or "exploratory" to some, more comprehensive, level that needs to be specified) should be identified, and eventually directions/guidance should be developed that will relate user-selected information and options (assumptions, parameters, inputs) to the expected relevance, reliability, accuracy, etc. of model estimates. For example, use of point estimates versus use of distributions for inputs and/or parameters, and use of default versus case-specific distributions, etc., are options that will influence model estimates. It is, in fact, the "risk ranking purpose and scope" associated with a given application that should determine such choices. It is especially important that for "comparative ranking" purposes of food-hazard pairs, the choices correspond to "equivalent" or, at least "practically equivalent," assumptions and levels of detail in the information used, to minimize biases in comparison procedures.

> **RESPONSE:**As indicated above in the response to Comment G-4-8, we recognize that the required information and guidance can vary depending on the data available to each user or organization hoping to use FDA-iRISK, and depending on the intended purpose of the resulting estimates. We will take this comment under consideration and address the needs as appropriate moving forward.

[**COMMENT 1-5-2**] It is noted that when a chemical hazard is present in multiple foods, users of iRISK will only be able to generate exposure, risk, and public health burden estimates for each food individually (when users have adequate information to support the use of the FDA-iRISK model). Users can also rank the public health burden of the foods involved but will not be able to

estimate aggregate exposure and overall public health burden due to the presence of such a chemical hazard in the food supply. Since in practice a chemical contamination often involves multiple foods, an understanding of aggregate exposure is needed to understand total risk. The ability to aggregate dietary exposure is important and should be a component of FDA-iRISK.

RESPONSE: Similar comment was made by another reviewer in Comment 1-1-6. We will take this comment under consideration and address the needs to model multiple foods and aggregate exposure prior to applying the dose-response model, as appropriate, moving forward in our efforts to expand the capacity of FDA-iRISK.

CHARGE QUESTION 2: COMMENTS AND RESPONSES

CHARGE QUESTION 2: *The FDA-iRISK model structure consists of a process module that enables the user to define initial conditions and select from among nine process types to describe changes in the prevalence and level of a hazard, as well as the unit size of food, at various process stages.*

CHARGE QUESTION 2.1: *The initial conditions specified in a process model include prevalence, concentration, and unit size (a fixed quantity of food, for example, the quantity of a consumer package or production batch). Are these characterizations of initial conditions appropriate and are they implemented appropriately in the model? If not, the reviewer should suggest how the characterizations might be improved.*

Noted Strengths:

[**COMMENT 2.1-1-1**] These characterizations are appropriate.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 2.1-2-1**] I think they are appropriate (see Nauta 2002).

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 2.1-3-1**] I found the options for describing initial conditions to be appropriate and properly implemented.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 2.1-5-1**] The description of the initial conditions (as described on page 4 of the Technical Documentation) and implementation in iRISK are appropriate.

RESPONSE: FDA thanks this reviewer for their comment.

Short-Term Action Items:

[**COMMENT 2.1-4-1**] The characterizations of initial conditions (prevalence, concentration, and unit size) are appropriate (at least for the "present state of development" of the iRISK modeling system), and they do appear to be implemented appropriately in the model. A suggestion related to specification of initial conditions would be to add a lognormal option to the distributions available for characterizing initial hazard concentration in the food.

RESPONSE: The addition of the lognormal distribution option is planned for the next version of the tool.

[**COMMENT 2.1-5-2**] The differences in the sequence of information provided between the Technical Documentation and the Workbook for Peer Reviewers created some challenges in

understanding iRISK. The Technical Documentation provided the process model information first then the hazard related modeling (i.e., dose-response, DALY, etc…), while the workbook (implementation) starts with hazard. This makes it very confusing and very challenging to read and follow initially.

> **RESPONSE:** As described in the response to Comment G-5-7, the Technical Documentation has been extensively revised, including the order in which concepts are presented. Some level of compatibility between these documents has been sought, though this is inherently limited by the fact that the two documents have entirely different purposes (step-by-step instruction versus understanding the mathematical basis of the tool). FDA plans to make the revised document available to users.

Longer-Term Action Items:

[**COMMENT 2.1-4-2**] Of course, characterizations of initial conditions will need to be enhanced with additional attributes if, in the future, the iRISK framework is enhanced with options for more mechanistically-based representations of the various physicochemical and biological processes involved in the exposure "sequence" leading from external dose (intake), to internal dose (uptake), to biologically effective dose (target tissue dose). Such attributes could be structural and physicochemical properties of the inhomogeneous food matrix potentially affecting the bioavailability of a chemical contaminant present within components of that matrix.

> **RESPONSE:** FDA-iRISK generates an estimate of the consumed (intake) dose that is consistent with the dose component of the dose-response model. The probability of adverse effect given response could be used to address internal dose and biologically effective dose. We agree that if future versions of FDA-iRISK add more stages to the exposure sequence, additional parameters will be required. In addition to evaluating potential new process types, we plan to evaluate other potential features for future development, such as linkage to an external physiological-based pharmacokinetic model to provide more mechanistically-based representations of exposure and the dose-response relationship.

[**COMMENT 2.1-4-3**] With respect to microbial contamination, characterization of inhomogeneities in the concentrations of microorganisms within the food should be incorporated in more refined (future) versions of iRISK components; an excellent summary of the issues associated with this problem and approaches to overcome them can be found in the ILSI Europe 2010 Report *Impact of Microbial Distributions on Food Safety*.

> **RESPONSE:** The FDA-iRISK tool allows a user-specified level of variation in the concentration of organisms *between units* of food (e.g., between-unit variability in concentration). It is assumed that microbial hazards are distributed randomly in each simulated unit of food and their presence in a sub-sample of the unit of food would follow a Poisson distribution (this is a simplifying assumption often made in published risk assessments). This assumption of homogeneity refers to the distribution within a unit of food. This is equivalent to the assumption that a unit of product is "well mixed."

While we agree with the premise that contamination of hazards can occur in pockets, there is often very little basis on which to specify the distribution and parameters to describe local (e.g., within unit) variations in concentration. We are aware of the ILSI Europe 2010 report, and plan to evaluate and, as appropriate, provide a means to describe clustering of microbial pathogens (i.e., non-homogeneous spatial distribution) in FDA-iRISK development.

CHARGE QUESTION 2: *The FDA-iRISK model structure consists of a process module that enables the user to define initial conditions and select from among nine process types to describe changes in the prevalence and level of a hazard, as well as the unit size of food, at various process stages.*

CHARGE QUESTION 2.2: *Are the process types in the model adequate to describe major relationships or outcomes at various process stages for the food-hazard pairs? If not, please explain.*

Noted Strengths:

[**COMMENT 2.2-2-1**] Yes (although, I cannot really judge this for chemical hazards).

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 2.2-3-1**] Based on somewhat limited experience in food processing, I found the available process types to be adequate.

RESPONSE: FDA thanks this reviewer for their comment.

Short-Term Action Items:

[**COMMENT 2.2-1-1**] The process types in the model are adequate to describe the major process steps, with the exception of microbial toxins, as chemical hazards cannot "grow."

RESPONSE: We agree that the available process types in FDA-iRISK do not provide a means to model microbial toxins in a process model starting with the microorganism which may produce toxin as a result of its growth in food. Currently, microbial toxins (such as histamine) can be modeled in FDA-iRISK using a process model starting with initial conditions for the toxin. The correlation between growth, population density and toxin production is more complex to model than modeling growth alone. We plan to evaluate and, as appropriate, provide a means to characterize toxin production in future FDA-iRISK development, including consideration of linkage to growth modules external to FDA-iRISK.

[**COMMENT 2.2-4-3**] It should be noted that the mathematical models describing the process types currently available in iRISK have limitations (such as ignoring critical *dependencies of processes on temperature*) that are also discussed in the answers to the questions that follow.

> **RESPONSE:** FDA-iRISK process type mathematical functions are described in detail in the Technical Documentation. We agree that users should be aware of the input parameters and assumptions made for each process type. While a process type, such as increase by growth, currently requires input of the extent of growth (log increase), it does not imply that the influence of process conditions such as storage time and temperature should be ignored. In fact, users may typically need to determine the log increase as affected by time and temperature using an external predictive model, and use the predicted growth as input in FDA-iRISK (see Chen et al. 2013, case study on *L. monocytogenes* in cantaloupe). We plan to add a clarification of this point in future revisions of the Technical Document. We plan to evaluate and, as appropriate, provide a means to characterize the effects of processing conditions such as temperature in future FDA-iRISK development, including consideration of linkage of predictive models to FDA-iRISK.

[**COMMENT 2.2-5-1**] The process stage types for chemicals are described in the Technical Documentation from pages 14 to 20. Section 2.4.1 "*Increase by Addition - Chemical*"—this section makes sense, but "M" on page 14 should be defined.

> **RESPONSE:** We have considered this comment in revising the Increase by Addition – Chemical section of the Technical Documentation. FDA plans to make the revised Technical Document available to users.

[**COMMENT 2.2-5-2**] Section 2.4.2 "*Decrease - Chemical*"—is this decrease due to some kind of treatment/removal process that is different from dilution? Please give an example for clarity.

> **RESPONSE:** The decrease step in a chemical hazard process model is designed to represent a situation in which the concentration of the hazard is reduced with no corresponding change to the unit quantity, whereas a dilution step results in both the specified concentration decrease and associated quantity increase. The decrease step typically is due to a treatment/removal process.

[**COMMENT 2.2-5-3**] Section 2.4.3.1 "*Pooling - Chemical*"—this reviewer does not understand what is intended here. How is this pooling different from dilution?

> **RESPONSE:** Dilution involves the addition of uncontaminated mass or volume to the system, such that the number of units is unchanged, the amount of hazard in each unit is unchanged, but the concentration of hazard is reduced in accordance with an increase in quantity. In contrast, pooling describes the combining of existing units, some which may be contaminated and some not. After pooling, the number of units is reduced as the size is increased, while the amount of hazard in each unit (and concentration) depends on the level in the pooled units and the fraction of pooled units that are contaminated.

[**COMMENT 2.2-5-4**] Similarly, Section 2.4.5.1 "*Partial Redistribution - Chemical*" and Section 2.4.5.2 "*Total Redistribution - Chemical*"—how are the changes in concentration from these processes different from changes in concentration due to pooling/dilution?

> **RESPONSE:** There is no change in unit quantity or number of units for the process types of partial or total redistribution. Rather, they describe a step where the existing contamination is redistributed among the existing units such that the prevalence increases, with a corresponding decrease in concentration among contaminated units.

[**COMMENT 2.2-5-5**] Explicit examples to demonstrate what is meant by each of these processes and to show the effective changes in chemical concentration in food during these processing steps would be very helpful for the reader to better understand the processing phenomena being described here.

> **RESPONSE:** Explicit examples may be included in future revisions of the associated documentation.

<u>Longer-Term Action Items</u>:

[**COMMENT 2.2-4-1**] The "process types" currently available in the iRISK modeling system for describing major relationships or outcomes at various "process stages" for the food-hazard pairs do not include explicitly changes associated with important factors such as *temperature, acidity, water and fat content, etc.* that could have substantial effects on the dynamics of either microbial or chemical contaminants. Such explicit considerations should be incorporated in "mechanism-driven," i.e., more refined (future) versions of relevant iRISK components.

> **RESPONSE:** At this time, FDA-iRISK relies on the user to characterize changes associated with these factors using the existing set of process types and, as appropriate, modeling the effect of factors such as time, temperature, pH, water activity, etc. outside of FDA-iRISK. FDA is considering developing additional process types or providing linkage to external modules in future releases.

[**COMMENT 2.2-4-2**] One major addition/improvement that is needed for chemical contaminants is the incorporation of *physicochemical transformation of the contaminant,* which could result to the formation of secondary chemical contaminants in the food items of concern.

> **RESPONSE:** We will evaluate and as appropriate address this in future version of FDA-iRISK.

CHARGE QUESTION 2: *The FDA-iRISK model structure consists of a process module that enables the user to define initial conditions and select from among nine process types to describe changes in the prevalence and level of a hazard, as well as the unit size of food, at various process stages.*

CHARGE QUESTION 2.3: *For microbial toxins where the process model would start with a microorganism in food while the hazard in the food at consumption would be a toxin, are the process types in the model adequate to describe major relationships or outcomes at various process stages involving microbial toxins? If not please explain.*

Noted Strengths:

[**COMMENT 2.3-3-1**] Outside my area of expertise.

[**COMMENT 2.3-5-1**] Aflatoxin was the example that was used in the workshop demonstration for peer reviewers. Based on this example, there was no processing step involved. Rather, the aflatoxin (hazard) levels were assumed to be present in food as consumed (tortilla). This reviewer assumed that if aflatoxin and corn (an ingredient of tortilla) is of interest, then the processing steps for microorganism in food would be implemented. This is due to the fact that mycotoxin levels in corn can be heterogeneous (cluster) and homogeneity (uniform distribution) cannot be assumed. In this context, the processing model for microbial hazards would be appropriate for microbial toxins.

RESPONSE: FDA thanks this reviewer for their comment.

Short-Term Action Items:

[**COMMENT 2.3-1-4**] Another consideration is the best before date. The closer the food is consumed to the best before date, the higher the levels of microbial toxins are expected to be. This will impact risk ranking, as it must be expected that consumers may consume up to and even beyond this date.

RESPONSE: A situation such as this could be addressed by using a distribution to represent growth between retail purchase and consumption of the food and its impact on the production of microbial toxins. The resulting distribution can be defined as ranging between the least production anticipated (i.e. consumed right after purchase) to the most production anticipated during this period (including exceeding the best before date). As described in the response to COMMENT 2.2-4-3, users may typically need to determine the increase in pathogen levels or microbial toxins as affected by consumer storage time and temperature using an external predictive model, and use the predicted log growth or the amount of increase in toxin concentration as input in FDA-iRISK.

Longer-Term Action Items:

[**COMMENT 2.3-1-1**] The model needs to account for growth of microbes and increases in microbial toxin levels in the production chain (from the field or farm or body of water, sorting and grading which may remove contamination by visual inspection, transportation and/or storage in silos, grain elevators, warehouses and/or processing site, manufacturing steps, storage and transportation, and consumer behavior prior to consumption). For aflatoxins in tortilla chips, this is not necessary, as the cooking of the corn in alkaline solution will likely destroy the microbe, so the concentration of aflatoxin in the tortilla chip is unlikely to increase after production. This would not apply for most other milled grain products (e.g., flour).

> **RESPONSE:** The process model as implemented in FDA-iRISK can be defined to represent the entire production and processing system of the food, or to represent the finished, ready-to-consume food, depending on the requirements of the model and available data. However, the current version of FDA-iRISK does not support a single integrated process model spanning both microbial and chemical hazards. This feature may be added in future releases.

[**COMMENT 2.3-1-2**] Processing steps for microbial toxins must account for the three types of toxins: those that grow solely in the field or ocean, those that appear only under storage, and those that grow both in the field and in storage.

> **RESPONSE:** Please see the response to Comment 2.3-1-1.

[**COMMENT 2.3-1-3**] With microbial toxins, some can be removed by visual inspection of the raw materials or finished products. In addition, these toxins can be distributed differently in different parts of the organism —if performing a ranking for flours, the prevalence and levels of a given toxin may be higher if considering whole grain flours, or partially whole grain flours, versus highly processed flours. The process diagram for microbial toxins must be a blend of all the processing steps in microbial and chemical hazards.

> **RESPONSE:** Please see the response to Comment 2.3-1-1.

[**COMMENT 2.3-2-1**] Microbial toxins are a bit complicated, as, indeed, they combine microbiology with chemicals. The actual hazard is a toxin, but you might need to model the microorganism that produces it first. The user should know where and when in the process (and food) the toxins are formed, and how much. The amount formed may depend on the specific strain of the microorganism, on its state, food conditions, etc. In iRISK, this can be summarized by just "adding" toxins at the right point in the process, but this demands substantial knowledge of the users. This is not a problem that iRISK can solve; the users must have the appropriate expertise

> **RESPONSE:** We agree that the current version of FDA-iRISK requires the user have the appropriate expertise. We plan to further develop capacity in the tool in the future to model microbial toxins.

[**COMMENT 2.3-2-2**] The choice of hazards is limited to microbial pathogen and chemical. The user does not have the option to choose that the hazard is actually a microbial toxin. This may be confusing for the user, and it might be helpful if the user was guided by iRISK in how to use it with a microbial toxin. The Technical Documentation doesn't refer to microbial toxins either, so this point is not very well explained to the user.

> **RESPONSE:** We plan to develop guidance on how to use FDA-iRISK to model microbial toxins in future revision of the documentation, in particular as additional capacity in the tool is developed in the future to model microbial toxins.

[**COMMENT 2.3-4-1**] The "process types" available in the current version of the iRISK modeling system for describing relationships or outcomes at various "process stages" involving microbial toxins have limitations similar to those described in the answers to Questions 2.1 and 2.2. These limitations should be addressed in future versions of the system with options for more realistic representation of the physics, chemistry and biology involved in "food contamination dynamics" (e.g., consideration of inhomogeneities of contamination within the food unit, effect of acidity, important attributes of the contaminant, whether it is hydrophilic or lipophilic, etc.).

> **RESPONSE:** We plan to evaluate and, as appropriate, develop additional process types that address these comments in future versions of FDA-iRISK.

CHARGE QUESTION 2: *The FDA-iRISK model structure consists of a process module that enables the user to define initial conditions and select from among nine process types to describe changes in the prevalence and level of a hazard, as well as the unit size of food, at various process stages.*

CHARGE QUESTION 2.4: *Are there additional process types that should be incorporated into the model for chemical hazards, microbial hazards, or microbial toxins? Is there any process type or function currently in the model that is not necessary and should be omitted for chemical hazards? If so, the reviewer should explain how to address such changes in the model.*

Noted Strengths:

[**COMMENT 2.4-1-1**] This has been addressed in Question 2.3.

[**COMMENT 2.4-2-2**] I don't think any process type or function should be omitted.

RESPONSE: FDA thanks this reviewer for their comments.

[**COMMENT 2.4-3-1**] No changes or additions that I can think of.

[**COMMENT 2.4-4-1**] The set of "process types" for chemical hazards, microbial hazards, or microbial toxins, which are currently incorporated in the iRISK framework, can be considered adequate at this stage of modeling system development.

RESPONSE: FDA thanks this reviewer for their comments.

Short-Term Action Items:

[**COMMENT 2.4-4-2**] However, what is problematic is the current formulation and parameterization of the models describing these processes, as discussed above, in the answers to Questions 2.1, 2.2 and 2.3 (see also below, answer to Question 3.2).

RESPONSE: Please see respective responses to similar comments under Questions 2.1, 2.2 and 2.3.

[**COMMENT 2.4-5-1**] For chemical hazards, the fate of a chemical in foods during the production, packaging, and transporting of foods and the impact on its concentration in foods are typically thought of as an increase or decrease in concentration due to various physical and chemical influences (i.e., heat, pH, reaction, partitioning into fat/water compartments, etc.). The terminology in iRISK (in the Technical Documentation) is awkward and, while the equations may address these phenomena, it is difficult to follow. As noted earlier, explicit examples for each of the processing phenomenon the author is trying to describe will help reader to fully understand if the chemical fate in food is adequately captured by the existing models/equations in iRISK.

RESPONSE: We plan to evaluate and, as appropriate, attempt to provide more examples in future revisions to the documentation.

[**COMMENT 2.4-5-2**] How does iRISK handle other chemical fate issues such as reaction/metabolites? If it does not, please explicitly state.

RESPONSE: FDA-iRISK does not explicitly handle chemical fate issues. The user is restricted to the available process types to describe such chemical transformations within the process model. The Technical Documentation will be revised to provide clarification of this point.

Longer-Term Action Items:

[**COMMENT 2.4-2-1**] I have worked with *Bacillus cereus*, which is a rather complicated hazard because it is spore forming. It may produce toxins in the food, and the dose-response relation is not known (this depends among other reasons on the enterotoxins formed). It will be quite difficult to use iRISK for a hazard like this. You need sporulation and germination models, a differentiation in populations/concentrations of vegetative cells and spores, different inactivation models, models for toxin formation, etc. But I don't think it is necessary to add those processes to iRISK right now. It may be considered for a future version.

RESPONSE: We acknowledge that spore-forming and toxigenic microorganisms are challenging to model for the reasons expressed by the reviewer. We are exploring methods to better characterize them in future versions of FDA-iRISK.

[**COMMENT 2.4-4-3**] A higher priority (than adding more processes to the system) at this point in time should be to improve the formulations of the existing process modules (taking into account, as needed, temperature effects, physicochemical transformations, etc.).

RESPONSE: As stated previously, FDA-iRISK process type mathematical functions are described in detail in the Technical Documentation. We agree that users should be aware of the input parameters and assumptions made for each process type. While a process type, such as increase by growth, currently requires input of the extent of growth (log increase), it does not imply that the influence of process conditions such as storage time and temperature should be ignored. In fact, users may typically need to determine the log increase as affected by time and temperature using an external predictive model, and use the predicted growth as input in FDA-iRISK (see Chen et al. 2013, case study on *L. monocytogenes* in cantaloupe). We plan to revise the Technical Documentation to add a clarification of this point. We plan to evaluate and, as appropriate, provide a means to characterize the effects of processing conditions such as temperature in future FDA-iRISK development, including consideration of linkage of predictive models to FDA-iRISK.

[**COMMENT 2.4-4-4**] For example, the process formulations described in Section 3.4 (pages 20-29 and in particular Tables 3.1 and 3.2 on pages 21 and 22) of the 2002 European Commission Health and Consumer Protection Directorate-General Report *Risk Assessment of Food Borne Bacterial Pathogens: Quantitative Methodology,* should be considered in future refinements of the iRISK system.

RESPONSE: See the response to COMMENT 2.4-4-3.

[**COMMENT 2.4-4-5**] These refinements should be considered in parallel with other high priority improvements, required by other aspects of the modeling system (e.g., dose-response functions for acute chemical exposures, systematic treatment of both variability and uncertainty in the various components of the system, etc.), as discussed in the following.

RESPONSE: Additional acute chemical exposure dose-response models and probabilistic characterization of uncertainty are being considered and developed as new features for inclusion in future versions of the tool.

[**COMMENT 2.4-4-6**] Consideration of additional "process types" can take place as the iRISK system further evolves into a more comprehensive system in the future.

RESPONSE: We concur with the reviewer and future versions may include additional process types.

CHARGE QUESTION 3: COMMENTS AND RESPONSES

CHARGE QUESTION 3: *The technical document provided for the peer review describes the functions or equations (Equations 1 through 54) that underlie exposure assessment and risk characterization for chemical and/or microbial hazards.*

CHARGE QUESTION 3.1: *Are any of the assumptions underlying these functions or equations (described in the technical document) unreasonable according to current modeling in which estimates of risk are generated? If so, please explain.*

Noted Strengths:

[**COMMENT 3.1-1-1**] The reviewer will not comment on all calculations related to microbial hazards, as the expertise does not extend to these types of hazards.

[**COMMENT 3.1-3-1**] I found the assumptions built into iRISK to be appropriate and reasonable.

RESPONSE: FDA thanks this reviewer for their comments.

Short-Term Action Items:

[**COMMENT 3.1-1-2**] For chemicals, the principle issues are in the calculation of disease burden, the probability of illness given a typical dose and the consumption pattern. This has been addressed in previous questions.

RESPONSE: We concur with the reviewer and recognize that there are many challenges. However, attempts have been made to conduct quantitative risk assessments for chemical contaminants in foods, e.g. with cancer endpoints from arsenic in apple juice (Carrington et al. 2013) and with non-cancer endpoints (fetal neurodevelopment and coronary heart disease) from methylmercury in commercial fish (FDA 2009). In these studies, assumptions were made and limitations and uncertainties were characterized along with risk estimates. We plan to conduct more case studies on chemical hazard risk scenarios, including attempting to replicate selected published risk assessments in FDA-iRISK as a means for validation.

[**COMMENT 3.1-1-3**] The issues are the following: most toxicological data for chemicals are incomplete, often inconclusive and contradictory, and, where available, are based on extrapolation from animal models;

RESPONSE: Please see the response to Comment G-1-7.

[**COMMENT 3.1-1-4**] The issues are the following: …it is not possible to relate the estimated number of total illnesses to actual health metrics from a given population as this information is not available (estimates are available at best);

RESPONSE: Please see the response to Comment G-1-8.

[**COMMENT 3.1-1-5**] The issues are the following: …the difficulty in linking illnesses from chronic exposure to a specific hazard-food combination or even a specific hazard in most cases (in the presence of other potential causes or sources of disease);

RESPONSE: Please see the response to Comment G-1-9.

[**COMMENT 3.1-1-6**] The issues are the following: …quantification of chronic risk for low levels of contaminants and low probability of health effects;

RESPONSE: Please see the response to Comment G-1-9.

[**COMMENT 3.1-1-7**] The issues are the following: …and differences between individuals in their susceptibility to chemical or microbial hazards.

RESPONSE: Please see the response to Comment G-1-11.

[**COMMENT 3.1-2-1**] I think they are correct (at least for the microbial hazards). It would be adequate to refer to other sources where process stage types and models are described and discussed, e.g., Nauta 2002, Nauta 2008, ILSI 2010, and ICRA (on www.foodrisk.org).

RESPONSE: Please see the response to Comment G-2-5.

[**COMMENT 3.1-4-1**] The Technical Documentation is essentially a brief annotated listing of the functions and equations (…equations 1 through 46…) used in the formulation of the various components of the iRISK system, with only minimal amount of text describing the variables and parameters that appear in these functions and equations. In most cases, there is no explanation, or even a reference to the existing literature, justifying why these particular functions and equations were selected. Specifically:

RESPONSE: Please see the response to Comment G-5-6.

[**COMMENT 3.1-4-2**] The entire Technical Documentation includes a single reference, specifically the USEPA 2012 *Benchmark Dose Technical Guidance.*

RESPONSE: The Technical Documentation has been revised to provide additional references and we plan to make the revised document available.

[**COMMENT 3.1-4-3**] In many of the subsections of the Technical Documentation, a single "Assumption" underlying the selection of the equation described in the subsection is included. However, the statement of the assumption is not accompanied by any discussion involving either the justification or the consequences of this assumption. Also, there is no discussion as to whether other assumptions could have been adopted, leading to potentially different risk estimates.

RESPONSE: We plan to revise the Technical Documentation to address these issues, including more discussion of assumptions underlying mathematical equations.

[**COMMENT 3.1-4-4**] Representative examples of assumptions that need to be justified (or that could be considered unreasonable in certain cases) are: The assumption of a constant-exponent for microbial increase by growth (U in Equation 4, Section 2.3.1, page 6).

RESPONSE: For process models that include microbial growth, the user is responsible to provide the total increase in the microbial population expected in the process step (including providing the increase in the form of a distribution to depict variability in the amount of growth). The user is free to use any available tool which may include complex relationships between temperature, pH, a_w, time, etc. in arriving at this level of microbial growth. As such, FDA-iRISK does not require the assumption of a constant exponent for microbial growth since the variable U can be described by a distribution. Additionally, a new feature of FDA-iRISK under development will allow the user to specify a maximum population density for microbial process models.

[**COMMENT 3.1-4-5**] Representative examples of assumptions that need to be justified (or that could be considered unreasonable in certain cases) are: …No explicit consideration of temperature (heating) effects in microbial growth rates (Section 2.3.1, page 6).

RESPONSE: Process stages associated with microbial growth are defined by the total growth over the duration of the stage, entered as a fixed value (point estimate) or distribution. In version 1.0 of FDA-iRISK, the user may use a distribution to take into account the effect of temperature or other conditions affecting growth. Similarly, reduction due to cooking or other types of thermal processing during a process stage would need to be represented using a distribution as appropriate.

[**COMMENT 3.1-4-6**] Representative examples of assumptions that need to be justified (or that could be considered unreasonable in certain cases) are: …The assumption of homogeneous mixing of microbial contamination in the food (no consideration of clustering).

RESPONSE: Please see the response to Comment G-1-18.

[**COMMENT 3.1-4-7**] Representative examples of assumptions that need to be justified (or that could be considered unreasonable in certain cases) are: …The assumption that the microbial decrease process can never remove the hazard completely of the system (Section 2.3.3, page 8), i.e., complete inactivation is not an option.

RESPONSE: The decrease process model which is used to describe microbial inactivation implements the decrease as a binomial process. Each unit of food has a non-zero probability of a surviving organism. The fact that cooking or other forms of inactivation may render most units of food free of any remaining contamination is explicitly accounted for by adjusting the prevalence of contaminated units.

[**COMMENT 3.1-4-8]** Representative examples of assumptions that need to be justified (or that

could be considered unreasonable in certain cases) are: …The assumption that evaporation does not add or remove microbial contamination from the system (Section 2.3.5, page 10) and may not be valid if heating is involved in the process.

> **RESPONSE:** The process stages in FDA-iRISK are intended to be used in a modular fashion with which to "build" a model representative of the impacts of food production and/or processing. If the evaporation process reduces the number of microbial cells or the amount of chemical contamination, for example, this could be modeled using a subsequent process stage of a decrease type (if the temperature of evaporation is high enough) or a growth type (if the temperature of evaporation supports growth). We plan to further clarify the use of combinations of process types to describe phenomena such as the one described by the reviewer in future versions of FDA-iRISK documentation.

[**COMMENT 3.1-4-10**] Representative examples of assumptions that need to be justified (or that could be considered unreasonable in certain cases) are: …The assumption that chemical hazards are totally inert and do not degrade by heating or chemical reactions and therefore are unaffected by acidity, water content, etc.

> **RESPONSE:** There is no implicit assumption in FDA-iRISK that chemical hazards are inert. Any effect of acidity, water content, or other conditions could be modeled by defining a "decrease" type process stage. We recognize that further clarification of this point may be helpful to users, and in the future may consider providing examples of how to use process stages to address some specific scenarios in the User Guide.

[**COMMENT 3.1-4-11**] Representative examples of assumptions that need to be justified (or that could be considered unreasonable in certain cases) are: …The assumption that evaporation (Section 2.4.4, page 17) does not involve any heating that could affect the chemical contaminant by causing some chemical transformation.

> **RESPONSE:** Please see the response to Comment 3.1-4-8.

[**COMMENT 3.1-4-12**] Representative examples of assumptions that need to be justified (or that could be considered unreasonable in certain cases) are: …The assumption of non-threshold linear responses for acute exposures to chemical hazards in food (Sections 4.4.2 and 4.4.3, pages 35 and 36, respectively).

> **RESPONSE:** The selection of dose-response models available in FDA-iRISK offers users a choice of different models and no assumption is made about the validity of any one model to describe a certain hazard. It is expected that the user would provide justification when choosing a particular model.

[**COMMENT 3.1-4-13**] While assumptions underlying iRISK components may not be generally "unreasonable" (as per the question), they are certainly not justified adequately. In many cases, the assumption employed represents the "simplest" choice, but even this fact is not stated explicitly; in other cases, the assumption poses limitations to the applicability of the model or introduces a certain bias in the estimates, but this is not stated explicitly either. It is certainly not

expected for the Technical Documentation for iRISK to be an extensive report or a monograph on chemical/microbial risk assessment. (In fact, the present answer could turn to a monograph if it was to discuss the justification, limitations and the available alternatives to the assumptions associated with each equation in the Technical Documentation).

RESPONSE: The Technical Documentation will continue to be revised.

[**COMMENT 3.1-4-14**] It is strongly recommended, however, to improve the Technical Documentation by including specific references, i.e., references to section/page and table or equation, of available national and international reports that offer guidance on risk assessment practice, in general, and on risk assessment for food contaminants, specifically. These references should include, among others (and in addition to the current single reference available in the Documentation, i.e., the USEPA, 2012 *Benchmark Dose Technical Guidance*), the following (detailed reference information can be found after at the end of the present review comments):

- USEPA. 1997. Guiding Principles for Monte Carlo Analysis;
- USEPA. 2000. Risk Characterization Handbook;
- European Commission. 2002. Risk Assessment of Food Borne Bacterial Pathogens: Quantitative Methodology Relevant for Human Exposure Assessment;
- WHO. 2006. Food Safety Risk Analysis - A Guide for National Food Safety Authorities;
- EFSA. 2006. Guidance of the scientific committee on a request from EFSA related to uncertainties in dietary exposure assessment;
- USEPA. 2008. Child-Specific Exposure Factors Handbook;
- IPCS. 2008. Uncertainty and Data Quality in Exposure Assessment;
- USEPA. 2009. Guidance on the Development, Evaluation, and Application of Environmental Models;
- IPCS/WHO/FAO. 2009. (Environmental Health Criteria 240) Principles and Methods for the Risk Assessment of Chemicals in Food;
- EFSA. 2009. Use of the Benchmark Dose Approach in Risk Assessment;
- RIVM. 2009. The Practicability of the Integrated Probabilistic Risk Assessment (IPRA) Approach for Substances in Food;
- ILSI Europe. 2010. Impact of Microbial Distributions on Food Safety;
- IOM & NRC, 2010. Enhancing Food Safety: The Role of the Food and Drug Administration;
- USEPA, 2011. Exposure Factors Handbook 2011 Edition;
- USEPA/USDA/FSIS. 2012. Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water; and
- USEPA. 2013. Dietary Exposure Evaluation Model User's Manual.

RESPONSE: We will take into consideration this suggestion in future revisions of the FDA-iRISK Technical Documentation, User's Guide and the Tutorial. We plan to explore different options of providing links to available national and international reports that offer guidance on risk assessment practice such as those suggested by the reviewer. Other resources of risk assessment guidance are also available, for example, through the JIFSAN-hosted site (www.foodrisk.org), which provides multiple sources (or links to) of

information of the type identified by the reviewer. This resource can be continually updated independently of FDA-iRISK for multiple uses, while being convenient to users of FDA-iRISK.

[**COMMENT 3.1-5-2**] *Consumption model for chronic exposure* – In Equation 29, "M" is defined as the average daily amount consumed during life stage "i." Is this usual intake or a mean based on a 2-day average intake of food (e.g., from NHANES)?

RESPONSE: The required input to describe chronic exposure to a foodborne hazard in FDA-iRISK is the average amount consumed daily over the extent of the life stage. In practice, the user will need to decide how to transform available data on consumption into a value or distribution for average daily intake.

[**COMMENT 3.1-5-3**] Given the terminology used by iRISK and given that the number of illness cases is calculated based on the number of consumers, the mean *per user* seems to be what iRISK is referring to. If the intent is to calculate LADDs for a cancer risk assessment, the conventional approach would rely on the mean *per capita* (when using NHANES 2-day average data). The mean *per user* and mean *per capita* should be the same for foods that are frequently consumed; however, these estimates can be vastly different for infrequently consumed foods. For infrequently consumed foods, the "usual" intake is needed for chronic intake estimate. And since usual intakes are difficult to derive, the mean *per capita* is often used as an approximate. The mean *per user* (derived based on short term 2-day intakes) would typically over estimate the long-term lifetime usual intake for foods not consumed on a daily basis. iRISK needs to be explicit with respect to what "M" is meant to represent and provide explicit guidance to users with respect to the appropriate food intake metric to be entered into iRISK.

RESPONSE: We concur with the reviewer on the distinction between mean *per user* and mean *per capita*; both estimates can be derived from analysis of NHANES data. Depending on the purpose of a risk assessment, one or the other estimate may be appropriate as input. We also concur that further guidance could be helpful to users and plan to evaluate and, as appropriate, provide existing references to users or add more information such as in the User Guide. The Technical Documentation has been revised to re-label M as A which remains defined as the average daily amount consumed during the life stage. Please see the response to Comment 3.1-5.2. We plan to make the revised document available.

[**COMMENT 3.1-5-4**] *Section 4 - Estimation of Cases of Illness – pages 27-44 of Technical Documentation* Under the dose calculation for both acute and chronic, please provide information on the dose units that are used in iRISK (e.g., mg/kg bw/day, ug/kg bw/day, etc.).

RESPONSE: The user is able to specify dose units when defining the dose-response models in FDA-iRISK. In addition, the user would need to adjust the parameters of the dose-response curve to be compatible with the dose units specified. The Technical Documentation has been revised to include additional discussion of dose units and we plan to make the revised document available.

[**COMMENT 3.1-5-5**] In this section, the dose-response models are detailed. However, the equations that describe how the mean risk of illness per person (in cases of chronic exposure) and the risk of illness per serving (in cases of acute exposure) are calculated are missing. Also, the equations to estimate the number of illnesses (annual no. of cases) are also missing. These equations should be provided with explicit examples of how the calculations are done. In particular, in the case of acute exposure, how body weight is (or is not) handled when dose is combined with dose-response to estimate the risk per serving should be explained.

> **RESPONSE:** We plan to revise the Technical Documentation to provide additional details and examples for these calculations. We plan to make the revised document available to users in the future.

Longer-Term Action Items:

[**COMMENT 3.1-1-8**] The consumption pattern, particularly for chronic risks, needs to take into account the relative importance of the given food commodity to other sources of the hazard, or how it compares to other observed levels of the hazard in foods. It also needs to take into account both "typical" and high-end consumers to generate the most conservative estimates.

> **RESPONSE:** We believe that FDA-iRISK accommodates the concerns expressed by the reviewer. The relative importance of the food commodity will be a combination of the amount of consumption and the level of contamination of the commodity, both of which are explicitly included in any FDA-iRISK model. In addition, the user is provided with the means to describe individual variability in the amount of consumption which will generate appropriately high levels of consumption or intake of contaminants according to the user's specifications. An additional component of FDA-iRISK to accommodate simultaneous intake of contaminants from multiple foods is under development.

[**COMMENT 3.1-2-2**] It would be even better if we could come to an agreement on a harmonization of terminology for the different process types!

> **RESPONSE:** We plan to continue to review and revise process types and their terminology in future version of FDA-iRISK.

[**COMMENT 3.1-4-9**] Representative examples of assumptions that need to be justified (or that could be considered unreasonable in certain cases) are: …The assumption that chemical hazards are distributed uniformly throughout the food (Section 2.4.3, page 16); pesticide residues on the surfaces of fruits and vegetables can be a counter-example; other counter-examples could be highly hydrophilic or lipophilic contaminants concentrating inhomogeneously within the food.

> **RESPONSE:** We concur with the reviewer regarding the assumption of uniformity and the specific example of surface contamination in some cases, and partitioning of certain contaminants because of inherent chemical properties. We plan to evaluate and, as appropriate, explain how available process types may be used to model these effects, or develop new features to describe these effects.

[**COMMENT 3.1-5-1**] *Section 3 – Consumption Models: Consumption model for acute exposure* – On page 21, it is noted that in iRISK, an acute exposure to a hazard is considered to refer to exposure during a single eating occasion (EO). While this single bolus dose scenario is possible (i.e., acute poisoning event), in chemical exposure and risk assessment, the short term exposure of interest could also be in the form of a single day or a weekly exposure. iRISK should allow for input of short term exposures other than the g/EO, such as an exposure dose calculated based on a 24-hr intake. These daily intake estimates are typically higher than the LADD calculated under the chronic exposure but below the bolus dose of g/EO.

> **RESPONSE:** In version 1.0 of FDA-iRISK, users can use the g/EO as a surrogate for g/24-hr, effectively creating a larger serving. FDA-iRISK assumes the same contamination level in all food consumed that day when determining the dose. We plan to review the option of providing other units of exposure for acute scenarios.

CHARGE QUESTION 3: *The technical document provided for the peer review describes the functions or equations (Equations 1 through 54) that underlie exposure assessment and risk characterization for chemical and/or microbial hazards.*

CHARGE QUESTION 3.2: *Are these functions or equations scientifically justified and biologically/ toxicologically sound for the purpose they are used in the model?*

Noted Strengths:

[none]

Short-Term Action Items:

[**COMMENT 3.2-1-1**] The functions may not be biologically/toxicologically sound because of the lack of human toxicological data and the extrapolation from animal data. Particularly in cases where human data may be available for some hazards, partial human toxicological data for some hazards and only animal data for other hazards, it will be difficult to do a meaningful comparison even taking into account these limitations.

RESPONSE: Please see the response to Comment G-1-7.

[**COMMENT 3.2-2-1**] Eq. 8: Why not give the probability of survival? That would simplify the notations.

RESPONSE: Equation 8 provides the probability of death of a single organism in a microbial decrease process type. It is provided in this format as the probability of death is required as part of equation 10 for prevalence. FDA may consider alternate representations for future versions of the document.

[**COMMENT 3.2-2-2**] Eq. 31: I do not understand how equation 31 is derived, and what it means. Being used to modeling acute risks, the concept is new to me.

RESPONSE: Equation 31 describes the calculation required to compute the lifetime daily average dose (LADD) consumed by an individual over their lifespan. It is derived by multiplying the average lifetime daily consumption of a food source by the mean concentration of the hazard in that food and by the fraction of servings that are contaminated. This dose is then applied to the dose-response model to determine the probability of response for that individual. It should be considered in combination with equation 26, which calculates the lifetime average daily consumption (LADC). The Technical Documentation has been revised to make the relationship between these two equations more explicit and we plan to make the revised document available.

[**COMMENT 3.2-2-3**] If I get it right, a chronic risk comes from an accumulated exposure, a sum of daily doses. If this dose varies for a person, the sum of the varying quantity over x days is well approximated by the sum of means over x days (the chronic accumulation). But between persons, the consumption will differ (some eat more and others eat less and also, some weigh more and others weigh less). If you have different age groups like in the aflatoxin example, you would expect that there is a correlation in weights for a person in different age classes. You cannot just take the mean between people here; the risk will be in the tail of this distribution. The different distributions that are used in the model are included in the calculations (and they should be), but it is not explained how. I, therefore, cannot judge whether it has been done correctly.

> **RESPONSE:** FDA-iRISK does not enforce correlation between the body weight of an individual in successive life stages. The LADD distribution represents the average daily dose across the lifespan for each person in the population, with no averaging across people in the population. Thus the upper tail of the LADD distribution will represent those individuals who experience a high intake in most or all life stages. As suggested by another reviewer in Comment 5.2-3-1 below, "knowledge of chronic consumption is very limited" and there is uncertainty in chronic food consumption modeling. We plan to evaluate and, as appropriate, further address the issue in future development of FDA-iRISK.

[**COMMENT 3.2-2-4**] I don't know what the time unit of a chronic disease is. Is a P, like in Eq. 39, the probability of response per day, per year or per life stage? This will make a difference.

> **RESPONSE:** In accordance with the dose-response model for chronic chemical exposures, the probability of response is per lifetime exposure. In FDA-iRISK, the length of the lifetime is determined by the total of the life stages included in the consumption model defined by the user.

[**COMMENT 3.2-3-1**] I found the equations and functions built into iRISK to be appropriate and reasonable; however, there were no reference sources provided for the equations used. For the dose-response models, at least a basic selection of reference sources must be provided. For the process models, reference to examples of previous applications would be helpful. I believe this will increase the confidence in the documentation and provide users with useful supplemental information.

> **RESPONSE:** The Technical Documentation has been revised to include additional references and we plan to make the revised document available.

[**COMMENT 3.2-4-1**] There are numerous issues with the variables/functions and equations used in iRISK and summarized in the Technical Documentation. Some general comments follow. Please see also answer to Question 3.1 above, as well as Table III of this review (Specific Observations on the Technical Documentation) for section-by-section comments on the functions and equations of FDA-iRISK.

> **RESPONSE:** The comments will be addressed individually below.

[**COMMENT 3.2-4-2**] Variables/functions representing biological/toxicological concepts and practices are introduced in the Technical Documentation without complete definitions, even when there are potentially multiple meanings to a general term.

RESPONSE: Please see the response to Comment G-5-6.

[**COMMENT 3.2-4-3**] The most important example of this situation is the concept of "dose" which is critical for any type of question/problem that may be addressed by iRISK. Probability distributions of doses, their parameters, dose-response models, etc. take different forms or values, correspondingly, depending on whether the external dose, internal dose, or tissue dose is used. The World Health Organization document *Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food*, chapter on *Dose-Response Assessment and Derivation of Health-Based Guidance Values* (IPCS/WHO/FAO, 2009) states:

"It is critical when performing dose-response analyses to have a clear concept of what type of 'dose' has been used in the available dose-response data. There are three basic types of dose that arise from scientific investigations; they are inter-related, and each of them can be used to express dose-response relationships. They are 1) the administered or external dose, 2) the internal (absorbed) dose and 3) the target or tissue dose.
External dose denotes the amount of an agent or chemical administered to an experimental animal or human in a controlled experimental setting by some specific route at some specific frequency. […] External dose, or external exposure, is frequently the dose metric that is used in observational epidemiological studies.

Internal dose is the amount that is systemically available and can be regarded as the fraction of the external dose that is absorbed and enters the general circulation. It is affected by absorption, metabolism and excretion of the chemical and can be derived from suitable toxicokinetic mass balance studies. The analytical method used in the toxicokinetic studies will determine whether the dose refers to the parent compound alone or the parent compound plus first-pass metabolites […]. Biomarkers of body burden, such as plasma concentrations or urinary excretion, are sometimes available in epidemiological studies.

The tissue dose is the amount that is distributed to and present in a specific tissue of interest. As for internal dose, the analytical method used in the toxicokinetic studies will determine whether the dose refers to the toxic entity, whether it be the parent compound alone or the parent compound plus first-pass metabolites […]. An additional consideration for tissue dose is whether the dose metric is the peak concentration or a time-weighted average, such as the area under the concentration–time curve."

External dose, internal dose, and tissue dose are often called intake, uptake, and target or effective dose, respectively. *It is strongly recommended that iRISK (and its Technical Documentation) clearly identify the type of dose in every equation, function, table, graph, etc. where the term "dose" appears.*

RESPONSE: Since the dose used for the dose-response model is generated by the process model in conjunction with a mass change function which takes into account the

amount consumed, FDA-iRISK considers "dose" to be the administered (intake) dose. It is important that the dose-response model reflects this, and this requirement will be made explicit in future documentation. We concur with the reviewer on the importance of "dose" unit clarification and plan to evaluate the option of providing the WHO document as a reference for users, or through other means such as a glossary of terms. Please see the response to comment G-1-13.

[**COMMENT 3.2-4-4**] Also, a Glossary of all major scientific terms appearing in the Technical Documentation (ideally with selected references to standard literature sources) would greatly enhance the usability (and value) of the document. *The development of such a Glossary is strongly recommended.* Definitions from the Glossary could also provide, in the form of hypertext linked to terms appearing in the on-line implementation of iRISK, a first level of on-line help for the user of the modeling system.

RESPONSE: We concur with the reviewer and will consider developing a glossary of major terms used, such as "dose" in Comment 3.2-4-3, in future development. Please also see response to Comment G-5-5.

[**COMMENT 3.2-4-5**] Though, in general, the equations ("component models") used in iRISK and summarized in the Technical Documentation are biologically/toxicologically sound, there are specific concerns regarding the currently available dose-response options for acute exposure to chemical contaminants. These options need to be clarified**.**

Furthermore, it is necessary, however, for the Technical Documentation to at least provide references for the source/origin of each equation, where full scientific justification for it would be available. (Examples of such references, mostly publicly available, are cited in the answer to Question 3.1).

RESPONSE: The Technical Documentation has been revised, citing more references, and we plan to make the revised document available.

[**COMMENT 3.2-4-6**] The range of problems that could potentially be addressed by iRISK is very wide. Currently, it is entirely up to the user to select (or to define) the equations and parameters that are appropriate for a particular application. Since these equations originate from a variety of scientific/technical fields (e.g., food science and engineering, exposure science, human behavior, consumer demographics, physiological dosimetry, human toxicology, public health, statistical methods of uncertainty and sensitivity analysis,etc.), even a user of iRISK with experience in multiple aspects of risk assessment may have to make decisions on issues outside her/his expertise. *There is therefore a need to provide more specific and comprehensive guidance on the relevance of different iRISK options to different problems.*

RESPONSE: We concur with the reviewer and will evaluate the option of developing more case studies and providing linkage to/developing guidance for users. We agree that in the current implementation of the tool, users require a wide range of expertise to fully define a risk scenario. Future revisions of the documentation may attempt to provide additional

guidance. It is also expected that individual users may need to rely on colleagues or work in groups to fully utilize FDA-iRISK.

[**COMMENT 3.2-4-7**] *It is important for the scientific notation to be consistent across the Technical Documentation* (as well as for all on-line-RISK applications). In the current version of the Technical Documentation, the symbol *di* is used to denote (fractional) concentration change in Chapter 2, while in Chapter 3 it denotes duration of life stage in years; furthermore, in Chapter 4, *d* is used to denote dose (presumably intake). As another example, σ denotes the microbial in Section 2.3.3 (page 8 of the Technical Documentation) and a standard deviation of the distribution in Section 4.5.1 (page 39).

RESPONSE: The Technical Documentation has been revised to reduce the number of repeated symbols used for different terms and we plan to make the revised document available.

[**COMMENT 3.2-4-8**] *Consistency of notation, as well as usability of the Technical Documentation, would be greatly facilitated by a comprehensive Table, listing alphabetically the notation for all variables, parameters, and functions appearing in the document (ideally with their corresponding dimensions or units).*

RESPONSE: We plan to evaluate and, as appropriate, adding a table as suggested to future versions of the document.

<u>Longer-Term Action Items</u>:

[COMMENT 3.2-5-1] The technical information provided for the review (iRISK 1.0 Technical Documentation, February 2013) describes the pre-determined structure of the risk model in its handling of the acute and chronic exposures. The document also provides the description of the dose-response models for acute and chronic exposure to chemical hazards. While the description of the available dose-response models in iRISK is clear, explicit examples under each type of dose-response model are needed to provide needed clarity to help improve the user's understanding of the usefulness of these dose-response models in iRISK.

RESPONSE: Explicit examples may be added to future versions of the document.

[**COMMENT 3.2-5-2**] In particular, while it is clear how cancer risk is handled in iRISK, it is not clear how non-cancer risk (from chronic exposure) is handled. More detailed description of how exposure dose is combined with the dose-response to estimate mean risk of illness and the number of cases when the health effect is non-cancer are needed.

RESPONSE: Additional details may be added to future versions of the document.

CHARGE QUESTION 3: *The technical document provided for the peer review describes the functions or equations (Equations 1 through 54) that underlie exposure assessment and risk characterization for chemical and/or microbial hazards.*

CHARGE QUESTION 3.3: *Considering the several food-hazard pair examples provided, are the equations or functions accurately implemented in the model? If not, please explain.*

Noted Strengths:

[**COMMENT 3.3-2-1**] In general they seem to be okay.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 3.3-2-4**] As the prevalence is modeled differently in the chemical hazard process type models, I think there is no problem there.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 3.3-3-1**] The examples appear to be accurately implemented. It is outside my area of expertise to independently replicate model functions.

Short-Term Action Items:

[**COMMENT 3.3-1-1**] This cannot be independently verified by the reviewer given the mathematical equations and the information provided in the technical documentation. There needs to be a better and clearer link made between the iRISK tool and the technical documentation to facilitate this comparison. The technical documentation has the equations ordered in a way that does not reflect the order in which the user is entering information into the model.

RESPONSE: As described in the response to Comment G-5-7, the Technical Documentation has been extensively revised, including the order in which concepts are presented. Some level of compatibility between these documents has been sought, though this is inherently limited by the fact that the two documents have entirely different purposes (step-by-step instruction versus understanding the mathematical basis of the tool). FDA plans to make the revised document available to users.

[**COMMENT 3.3-2-2**] I think I found an inaccuracy in the decrease model for microbial risks. The decrease d_i (page 8) is the log reduction, which may vary. It is not clear to me per what it varies: per food unit or per model run? Presumably, it is per food unit. In that case, you sample a d_i for every sampled C_{i-1} (and M_i), let's say for iteration j you have $d_{i,j}$ which, using Eqs. 7-9, allows you to calculate $C_{i,j}$ based on $C_{i-1,j}$ and $M_{i,j}$. But how is P_i calculated? According to Eqs. 8 and 9, ρ_j and σ_j vary as well, per food unit, so the prevalence should also vary per food unit in Eq. 10. But that cannot be because the prevalence is not a characteristic of a single food unit, but

of the population of food units. It does not have a distribution (see my remark, page 3 under Section III) but a value: the percentage of not contaminated units. If you interpret $P_{i,j}$ as the probability that j is not contaminated, the prevalence that you are after is the mean $P_{i,j}$ over all j; this is a single value and not a distribution. Eq. 10 should read: $P_i = P_{i-1} * \text{Mean}[(1-\rho)^{\sigma}]$

> **RESPONSE:** When applied to the results of process stages, the term "prevalence" refers to the probability of contamination of units of food for a given sample, i. The Technical Documentation has been revised to make this more explicit. In addition, the correct expression of Eq. 10 should be $P_i = P_{i-1} *(1-\rho^{\sigma})$, which is how it is implemented in the tool. We have revised the Technical Document and corrected this typo.

[**COMMENT 3.3-2-3**] Similar things may go wrong in the pooling model.

> **RESPONSE:** Please see response to Comment 3.3-2-2. The Technical Documentation has been revised to provide further clarification on the type of pooling that is being described by the process type currently implemented in the tool. As indicated above, we plan to make the revised document available to users.

[**COMMENT 3.3-4-1**] This question could be interpreted at different levels: Indeed, to literally respond to a question inquiring whether "equations or functions [are] accurately implemented in the model," would require access to the full code and parameters that translate the assumptions of the model and the mathematical formulations of its components into the executable code that performs simulations. Since this is not possible, we should interpret the question as focusing on how appropriate/relevant were the equations and functions used within the "examples provided" for the software demonstration (Workbook for Peer Reviewers, Implementing Chemical Risk Scenarios in iRISK; February 26, 2013), or for those contained in the online iRISK 1.0 User Guide (Document Version 1.1; October, 2012). Various issues among those raised in the answers to Questions 3.1 and 3.2 above, of course, apply to the three risk scenarios presented in the Workbook for Peer Reviewers ("Implementing Chemical Risk Scenarios in iRISK"), i.e., (1) chronic exposure to a chemical hazard: aflatoxin B1 in tortilla chips; (2) acute exposure to a chemical hazard: histamine in scombroid tuna; and (3) acute exposure to a chemical hazard: ammonia in frozen pizza. The examples are interesting and have the potential of being very informative, especially for new users for iRISK; however, the selections of inputs and parameters are problematic. For example, the chronic exposure scenario assumes a fixed value for average daily consumption and a uniform weight distribution for each life stage (Population Group) of the consumer population considered (e.g., page 21 of the Workbook). While the use of any reasonable fixed value for daily consumption could be useful in examining various "what if" scenarios, there is absolutely no reason to use such unrealistic distributions of body weight for the different life stages when so much information is publicly available to characterize these distributions (including the summary information, that can be used to input empirical distributions, contained in the two *USEPA Exposure Factor Handbooks* (for children and for the general population).

> **RESPONSE:** As noted in the peer review workbook the examples provided were intended to function only as illustrations of the use of the tool and so the inputs listed may not necessarily provide faithful representations of the risk. We concur with the reviewer that

daily consumption may vary, and body weight may not follow a uniform distribution. The scenarios may be revised in future releases.

[**COMMENT 3.3-4-2**] Another serious concern is the use of a Non-Threshold Linear Dose-response assumption for example (3).

RESPONSE: Please see the response to Comment 3.3-4-1.

[**COMMENT 3.3-4-3**] The meaning of the calculated DALY values for the acute exposures of example (2) for the total US population, on page 34 of the Workbook, and of example (3) for children of ages 6-12, on page 30 of the Workbook, requires further thought for an appropriate interpretation (if any).

RESPONSE: Please see the response to Comment 3.3-4-1.

[**COMMENT 3.3-5-1**] As noted above, there are a number of dose-response models for acute and chronic exposure described in the Technical Documentation and implemented in iRISK. However, the equations that combine the estimated dose to the dose-response and estimate the number of cases are missing, so it is difficult to know how iRISK implements these dose-response models in practice.

RESPONSE: While we believe that all required equations were included, the Technical Documentation has been revised to provide additional clarification of how FDA-iRISK applies the estimated dose to calculate the probability of illness using the dose-response functions to estimate the number of cases. We plan to make the revised document available.

[**COMMENT 3.3-5-2**] More detailed explanation and examples on how the dose-response models are used to estimate risk of illness for non-cancer effects (due to chronic exposure) for each of the available dose-response models in iRISK would help the reader to better understand how these models are implemented.

RESPONSE: Additional examples may be added to future versions of the documentation.

Longer-Term Action Items:

[none]

CHARGE QUESTION 3: *The technical document provided for the peer review describes the functions or equations (Equations 1 through 54) that underlie exposure assessment and risk characterization for chemical and/or microbial hazards.*

CHARGE QUESTION 3.4: *The technical document describes two new features: "positive distributions" and "stability analysis." Are these features adequate to address the intended computational or model convergence issues? If not, please explain.*

Noted Strengths:

[**COMMENT 3.4-1-1**] This is beyond the expertise of the reviewer to comment on.

[**COMMENT 3.4-3-1**] I agree that these features are appropriate and adequate to address computational and model convergence issues.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 3.4-4-1**] The decision of the developers of FDA-iRISK to employ (strictly) positive distributions (positive binomial and positive Poisson) for the analysis of microbial hazards is reasonable. It could be argued that this decision is not a formally necessary one, since fractional values of the hazard concentration in a stochastic modeling framework can be interpreted as being the values of probability of having a microorganism in the volume of the unit food quantity considered.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 3.4-5-1**] No comment here.

Short-Term Action Items:

[COMMENT 3.4-2-1] The two features are fit for purpose. For transparency, I would like to see the equations for the positive binomial and the positive poisson in the documentation.

RESPONSE: We have revised the Technical Documentation to provide further description for positive-only binomial and Poisson distribution. We concur with the reviewer and plan to add these equations in future versions of the document.

[**COMMENT 3.4-2-2**] The stability analysis could, by accident, give an unjustified stability result. Have the iRISK authors checked that? Well, I don't expect major problems here anyway.

RESPONSE: We have reviewed the algorithm for stability analysis and revised the Technical Documentation to provide further description on how the algorithm works. We plan to make the revised document available. We plan to modify the algorithm for

implementing Addition-type process stages to more effectively handle rare events that might previously have affected model stability.

[**COMMENT 3.4-4-2**] However, it is not clear how this positivity assumption, as described in the text of Section (Chapter) 6 (page 46 of the Technical Documentation), is consistent with the cumulative probability graphs of the exponential and Beta-Poisson distributions shown in Figures 5 and 6 of Section 4.3 (pages 31 and 32 of the Technical Documentation).

RESPONSE: We agree that there is the potential for inconsistency between the assumptions underlying the Beta-Poisson distribution and the definition of contamination within FDA-iRISK (specifically the requirement for at least one organism per contaminated unit). We are considering several options to address this including i) the addition of a Beta-Binomial dose-response type, ii) clarification of the technical documentation with respect to the application of the Beta-Poisson distribution, and iii) the clarification that doses of less than one organism will not be generated by FDA-iRISK.

[**COMMENT 3.4-4-3**] On a different note, it could also be argued that the arguments provided in Chapter 6 appear more relevant to defining a truncated distribution, i.e., a distribution defined over a domain of events that do not include microbial hazard concentration values less than unity.

RESPONSE: We agree with the reviewer that the arguments provided in Chapter 6 of the Technical Documentation are similar to the concept of truncation. However, the overall process of accommodating the need for one organism per contaminated unit includes adjustment of the concentration combined with adjustment of the probability of contaminated units to avoid the loss of contamination that would be associated with simple truncation.

[**COMMENT 3.4-4-4**] It should also be pointed out that on page 8 (Section 2.3.3) of the Technical Documentation the reader is referred to "the chapter on Positive Distributions for a description of the positive binomial function;" however, the only description that can be found in Chapter 6 is essentially that the distribution is positive.

RESPONSE: We plan to elaborate on the discussion of these functions in a future revision of the Technical Documentation to make the calculations more transparent.

[**COMMENT 3.4-4-5**] Regarding the second part of the present Question, i.e., the "stability analysis," it could be stated that the actual focus of the corresponding Section (Chapter 7) on page 47 of the Technical Documentation is a Monte Carlo simulation convergence criterion. In general, stability analysis of a Monte Carlo method refers to the systematic study of the "observed numerical changes in the characteristics (i.e., mean, variance, percentiles) of the Monte Carlo simulation output distribution as the number of simulations increases" (quoted from USEPA 1997; similar definitions can be found in any relevant reference, e.g., Kroese et al., 2011; Meyn et al., 2009). However, the procedure described in Chapter 7 of the Technical Documentation considers only fractional changes in the mean of the total calculated DALYs to

decide whether "the simulation is assumed or not to have or not converged." Clearly, the focus is on establishing reasonable convergence criteria and not on the analysis of the dynamics of the numerical scheme or the optimization of convergence-related parameters. The rules that are used to terminate the simulation based on the fraction of the DALYs are reasonable (cumulative mean changes by less than 1%) but essentially practical/empirical. Therefore, a more appropriate title to Chapter 7 would be "Evaluation of Convergence for the Monte Carlo Simulation," or something similar.

> **RESPONSE:** We agree with the reviewer's characterization of the material in Chapter 7 and plan to revise the title in future versions of the Technical Documentation.

Longer-Term Action Items:

[none]

CHARGE QUESTION 4: COMMENTS AND RESPONSES

CHARGE QUESTION 4: *A key feature of FDA-iRISK is the ability to compare both chemical and microbial risks. The model reporting includes results with different metrics. In addition to the mean risk of illness and the total number of illnesses, the annual DALY is used. With this in mind:*

CHARGE QUESTION 4.1: *Comment on the appropriateness of using the annual DALY and the strengths and limitations of the implementation of this metric in the model for chemical hazards.*

Noted Strengths:

[**COMMENT 4.1-3-1**] Strengths: In the typical practice of chemical risk assessment for non-cancer health effects, actual risk estimates are not developed and consequently direct comparisons to other chemicals or hazards is not possible. Therefore, the use of the DALY facilitates the comparisons of chemical and microbial risks for outcomes where the DALY is known or can be developed.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 4.1-2-1**] The annual DALY is a generic health measure that is well suited for chemical and microbiological risks. As always, the user should be aware of its limitations, like the subjectivity of the severity weights, and its strong tendency to weigh risks for elderly people less as risks for children, so (chronic) health problems of elderly people will get less weight than those of young people. But in my view, it is appropriate here.

RESPONSE: FDA thanks this reviewer for their comment.

Short-Term Action Items:

[COMMENT 4.1-1-1] The annual DALY is a problematic tool for risk ranking of chemical hazards. The principal strengths of this tool is that it provides a standardized means of calculating a risk score using specific types of user-defined inputs (assuming that the user is very consistent in what is considered in these inputs) and it is applicable to general and specific populations. The limitations of the annual DALY (rather than the inputs into calculating the DALY, which have been addressed earlier) are that DALY scores could not be computed for the majority of chemical hazards that result in chronic effects due to the lack of available human toxicological or exposure data, difficulty in determining the probability of illness, and the lack of context for these DALY values.

RESPONSE: On theoretical grounds, the DALY was considered one of the most appropriate metric on which to rank illnesses caused by microbial hazards and those caused by chemical hazards (Havelaar and Mesle 2003, Murray et al. 2012, Havelaar et al. 2012). In practice there is currently less scientific literature available for DALY valuations applied to chemical hazards compared to microbial hazards. FDA-iRISK

permits the user to define the expected health impacts of chemical exposures and their probability, document the rationale for the values used, and apply a single approach consistently across chemical hazards considered within the tool. As new data become available, values and assumptions can be refined such that the resulting risk estimate and ranking improve.

[**COMMENT 4.1-3-2**] The related limitations are:

- Not all potential chemical contaminants can be modeled because there are many chemical hazards where health effects information is derived from toxicological studies and may not have an equivalent in clinical or epidemiological literature (e.g., body or organ weight change); and
- Not all health effects or outcomes have a DALY.

Therefore, the universe of chemicals that can be assessed is limited to those where health effects information is amenable to DALY development.

RESPONSE: See response to Comment 4.1-1-1, above.

[**COMMENT 4.1-4-1**] It would be beyond the scope of the present review to address the general strengths and limitations of the implementation of the DALY (the term "annual DALY" seems redundant) as a public health metric for environmental (including food contamination) risks. An extensive—and growing—amount of literature exists on the subject (e.g., Anand and Hanson, 1998; Gold et al., 2002; Arnesen and Kapiriri, 2004; Murray et al., 2012; Ishak et al., 2013; etc.). However, while for well-defined health endpoints involving either microbial exposures or chronic chemical exposures, the use of DALYs as a metric of public health impact appears reasonable, its application to acute exposures and, in particular, to chemical contaminants needs substantial clarification.

RESPONSE: The Technical Documentation has been revised to include a discussion of health metrics such as the DALY and we plan to make the revised document available. We plan to further evaluate the literature on DALY including the references suggested by the reviewer and further address this issue as appropriate (including the terminolofy "annual DALY").

[**COMMENT 4.1-4-2**] The Technical Documentation for iRISK states that (Section 3.1, Acute Exposure, page 21) "[t]he mean risk of illness per serving is then multiplied by the user-specified annual number of servings consumed (again from the Consumption Model) to predict the number of cases per year. Each case is assigned a value for burden (in Disability Adjusted Life Years: "DALYs", or in cost of illness) and, in this way, the overall burden for the exposure is calculated. (This value for annual burden is the basis of the rankings.)" The "acute-to-annual" connection can be confusing, especially when the term acute is used to describe multiple, re-occurring, exposures within an annual period. Since iRISK does not consider biologically-based toxicokinetics and toxicodynamics to identify in-tissue residence time distributions of chemicals (or their metabolites), it does not provide a mechanism for assessing the time scales and frequencies that "separate" repeated acute from chronic exposures.

RESPONSE: FDA-iRISK requires users to specify the number of eating occasions per year for acute hazards and considers that the effect of 10 (for example) sequential acute exposures to one person are equivalent to the effect of the same acute exposure to 10 people, i.e. acute exposures are assumed to act on a "blank slate". This distinguishes acute chemical exposure from chronic chemical exposure, which assumes that each individual consumer is, in effect, exposed to a certain intake of chemical each day of the lifetime. We plan to evaluate whether it would be feasible to consider sub-chronic chemical exposures or multiple repeated acute exposures in FDA-iRISK.

[**COMMENT 4.1-4-3**] It should also always be kept in mind, when interpreting estimated DALY values, that they are population-based metrics and any attempts to "translate" them for relevance to individuals within the population can be very misleading.

RESPONSE: We agree that the DALY is a population-based health metric.

[**COMMENT 4.1-5-1**] The DALY is a useful and convenient means to normalize the impact of microbial and chemical risk on public health for comparison purposes. The main limitation with the use of DALY in chemical risk assessment is the lack of DALY values for toxicological endpoints without any direct clinical manifestation (e.g., frank effects, such as liver cancer, heart diseases, diabetes, etc.). Without published DALY values for an effect, the value assigned by a user of iRISK will be based on the user's judgment and bias.

RESPONSE: Please see the response to Comment 4.1-1-1.

Longer-Term Action Items:

[**COMMENT 4.1-5-2**] As noted earlier, since iRISK is a modeling platform and the user is required to input data/information, the "garbage in/garbage out" is a real consideration with using iRISK. As such, the narrative and documentation of the source and quality of the input data are an important aspect of iRISK that need to be systematically tracked. Perhaps, a qualitatively tracking of data quality for each model component and overall quality indication (combined for all model components) can be incorporated into iRISK and the output in the final report.

RESPONSE: We plan to consider developing this feature for future releases.

CHARGE QUESTION 4: *A key feature of FDA-iRISK is the ability to compare both chemical and microbial risks. The model reporting includes results with different metrics. In addition to the mean risk of illness and the total number of illnesses, the annual DALY is used. With this in mind:*

CHARGE QUESTION 4.2: *Comment on the appropriateness of available options for microbial and chemical dose response functions in the model and how they are used, as well as other dose response functions for chemical or microbial hazards that might be included as templates.*

Noted Strengths:

[**COMMENT 4.2-1-1**] These functions are appropriate and concur with scientific literature in this area.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 4.2-2-1**] For microbial risks, the choice of dose response models is appropriate. (I wouldn't use the non-threshold linear myself, but the tool has to be flexible.) I cannot judge this for the chemical risks.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 4.2-3-1**] I believe that the iRISK model includes the most common dose-response functions for both chemical and microbial hazards.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 4.2-4-1**] The microbial dose-response functions represent standard (and appropriate) selections, consistent with current national agency guidance and recommendations, as summarized in USEPA & USDA. 2012.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 4.2-4-3**] The chronic dose-response functions for chemical contaminants are generally consistent with the recommendations in USEPA. 2012. *Benchmark Dose Technical Guidance. US Environmental Protection Agency. EPA/100/R-12/001* and the models implemented in the USEPA *Benchmark Dose Modeling Software.* These dose response functions (models) should be considered appropriate.

RESPONSE: FDA thanks this reviewer for their comment.

Short-Term Action Items:

[**COMMENT 4.2-4-4**] However, the selection of the dose-response models for acute exposures to chemical hazards requires justification. The Technical Documentation should provide specific references to the data sources that support the selection of the four acute dose-response functions available in iRISK (Section 4.4, pages 33-37 of the Technical Documentation), i.e., the step threshold, non-threshold linear, linear by slope, and threshold linear.

> **RESPONSE:** This section of the Technical Documentation may be revised in future releases.

[**COMMENT 4.2-4-5**] It is particularly important to explain the rationale of the two non-threshold linear responses. It is also important to adequately explain the specific physiological endpoints that are affected by these acute exposures (gastrointestinal, neurobehavioral, cardiovascular, hepatobiliary, renal, etc.).

> **RESPONSE:** Please see the response for Comment G-4-5. The primary contribution of FDA-iRISK is to appropriately combine (structurally, and mathematically) the user's assumptions into an estimate of risk, assuming that the user's inputs are valid. Nonetheless, we agree with the reviewer regarding the need for further guidance or case studies and will take this suggestion into consideration in future efforts for FDA-iRISK development and outreach.

[**COMMENT 4.2-4-6**] A clear distinction of real acute exposures versus multiple repeated acute exposures over time needs to be made and effects of dose rate and frequency need to be explicitly addressed.

> **RESPONSE:** Please see the response to Comment 4.1-4-2.

[**COMMENT 4.2-5-1**] The Technical Documentation provided four dose response models for acute exposures to chemical hazards: 1) step threshold, 2) non-threshold linear, 3) linear by slope, and 4) threshold linear. Models 2 and 3 are effectively the same dose response, so this reviewer does not understand why the distinction is being made. Examples of chemicals that fit into these four distinct dose response models are recommended to be added to further the understanding of the reader of the Technical Documentation.

> **RESPONSE:** Please see the response to Comment 4.2-4-5. Regarding models 2 and 3, we agree with the reviewer that they represent the same dose-response. We provide two formats to allow users flexibility in parameterization depending on data available.

[**COMMENT 4.2-5-2**] …Further, since the conventional practice for non-cancer risk assessment is to either compare an estimated daily dose to a reference dose, RfD, or calculate a margin of exposure (MOE), i.e., NOAEL/daily dose, an explanation of how iRISK differs from this conventional approach is needed.

RESPONSE: Evaluating chemical exposures based on the RfD or the MOE does not provide any information as to the health impact to be expected if the threshold is exceeded. Such an approach is incompatible with ranking based on predicted health effect. FDA-iRISK assumes that acute and chronic exposures to chemical and microbial hazards result in measurable health impacts that can be meaningfully ranked. Although sound, in practical terms there are acknowledged challenges in chemical risk assessment that transcend FDA-iRISK. One of these relates to the level of risk to be expected from exposure to chemicals that result in non-cancer health impacts. Another challenge relates to exposure limits (e.g. RfDs) that have been derived from outcomes of very different severities (e.g. cancer at one extreme and changes in liver enzymes or in vitro assays which change gene expression at the other).

[**COMMENT 4.2-5-3**] For chronic exposure to chemical hazards, the Technical Documentation provided 10 models, which were adopted from the U.S. EPA benchmark dose modeling software. These models are adequate when addressing cancer risk and when there are adequate data for non-cancer risks. Again, since the conventional practice for non-cancer risk assessment is to either compare an estimated daily dose to a reference dose (RfD) or calculate a margin of exposure (MOE), i.e., NOAEL/daily dose, an explanation of how iRISK differs from this conventional approach is needed.

RESPONSE: Please see the response to Comment 4.2-5-2. The Technical Documentation and or User Guide may be revised to provide this explanation in future revisions.

Longer-Term Action Items:

[**COMMENT 4.2-4-2**] *Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus of Food and Water. Prepared by the Interagency Microbiological Risk Assessment Guideline Workgroup - USEPA and USDA. EPA/100/J-12/001; USDA/FSIS/2012-001.* This document lists additional dose response functions for microbial hazards that could be included as templates in future versions of iRISK.

RESPONSE: We plan to add the Weibull, Probit and Lognormal Probit dose-response models to the next release of FDA-iRISK.

[**COMMENT 4.2-4-7**] It should be mentioned that risk assessments for acute chemical exposures (though mostly driven by inhalation data) have typically employed probit lognormal and Weibull dose-response distributions (e.g., Krewski & Franklin, 1991; Covello & Merkhoher, 1993; Crawford-Brown, 1997; Hayes 2007; etc.). *It is strongly recommended that these two distributions be incorporated in iRISK as dose-response options for acute exposures to chemicals.*

RESPONSE: Please refer to the response to Comment 4.2-4-2.

CHARGE QUESTION 4*: A key feature of FDA-iRISK is the ability to compare both chemical and microbial risks. The model reporting includes results with different metrics. In addition to the mean risk of illness and the total number of illnesses, the annual DALY is used. With this in mind:*

CHARGE QUESTION 4.3: *Overall, are the results generated appropriate for comparing chemical (acute and chronic exposures) and microbial risks and risk ranking purpose? If not, the reviewer should explain other results and/or analyses that are needed.*

Noted Strengths:

[**COMMENT 4.3-2-1**] The DALY is a good health measure to compare different risks, and outcomes expressed in DALY can be used to rank risks.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 4.3-3-1**] I found the results generated are appropriate for comparing and ranking risks.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 4.3-4-1**] Given the answers provided to Questions 3.1 to 3.3 and 4.2, the answer to the present question needs to be appropriately qualified. So, it can be stated that, with careful selection of inputs, parameters, and other model options, FDA-iRISK can generate results appropriate for comparing risks from chronic chemical exposures and microbial risks and perform relevant risk tasks.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 4.3-5-1**] The FDA-iRISK model generates ranking of food-hazard pairs via a pre-determined model structure consisting of food, hazard, population of consumers, process module describing the introduction and fate of the hazard up to the point of consumption, consumption patterns, dose-response curves, and burden of disease metric. The overall model construction is logical for the stated purpose of FDA-iRISK, which is to generate *rankings of food-hazard pairs*.

RESPONSE: FDA thanks this reviewer for their comment.

Short-Term Action Items:

[**COMMENT 4.3-1-1**] The results (i.e., DALY scores) do not appear to be appropriate for comparing chemical and microbial risks and risk ranking. In this reviewer's opinion, the DALY score cannot be accurately computed for most chronic chemical hazards (due to a lack or incomplete human toxicological and/or exposure data) or for microbial toxins (as the model does not account for microbial growth in food associated with microbial toxins). Where it could be

calculated, the DALY score is entirely dependent on the user-defined inputs. The user-defined inputs must rely on a broad base of prevalence data and take into account other factors, such as new regulations and/or testing activity; otherwise, the DALY score may be unduly biased by one or more atypical studies.

> **RESPONSE:** FDA-iRISK provides a bottom-up method of predicting the number of cases of illness resulting from chronic chemical exposure. There are known challenges with evaluating chronic chemical exposures, as well as developing dose-response models for those exposures, however the soundness of the predictive model itself is independent of these challenges. Given the number of predicted cases, the resulting DALY score depends only on the value of DALY per case, which can be calculated transparently within the tool itself. In this sense FDA-iRISK cannot be said to perform more poorly than other predictive methods in the context of chronic chemical risk assessment. With regard to modeling microbial toxins, currently users can develop a process model starting with initial conditions describing the prevalence and concentration for the microbial toxins. We recognized that it is more complex to develop a process model starting with the toxin-producing organisms, and we will consider this as a potential area of development for FDA-iRISK.

[**COMMENT 4.3-2-2**] However, iRISK does not offer any tool to indicate whether the difference in ranking is "significant." Some type of uncertainty analysis would be helpful when risk ranking is used to compare risks (see below, Question 6).

> **RESPONSE:** We plan to develop a new feature that allows for quantitative descriptions of uncertainty, or so-called Second Order Monte Carlo simulation, for inclusion in future versions of the tool.

[**COMMENT 4.3-3-2**] However, I recommend that the scenario ranking summary report include the Hazard Metric or health effect relevant to each scenario included in the report. One problem I see in implementing this recommendation is that the health effect information is not always captured in the Hazard Metric field, sometimes it is part of the Hazard description and, in some of the examples, it is assumed, i.e., a Hazard Metric of "*Salmonella* DALY" does not actually describe Salmonellosis.

> **RESPONSE:** The individual health outcomes contributing to the total DALY value can optionally be included using the "Compute from Health Endpoints" feature of FDA-iRISK. These endpoints would then be included in the ranking report. The user can also include detailed descriptions in the notes associated with the Health Metric for inclusion in the report. Also of note, we have changed "Hazard Metric" to "Health Metric" in the Technical Documentation to more accurately describe the concept.

[**COMMENT 4.3-4-2**] *The issue of risks from acute chemical exposure needs to be further clarified* (see answer to Question 4.2).

RESPONSE: The primary contribution of FDA-iRISK is to appropriately combine (structurally, and mathematically) the user's assumptions into an estimate of risk, assuming that the user's inputs are valid. Nonetheless, we agree with the reviewer regarding the need for further guidance or case studies related to the choice of dose-response models for acute chemical exposures, and will take this suggestion into consideration in documentation, and other future efforts for FDA-iRISK development and outreach. Please see the response for Comment G-4-5 for additional information.

[**COMMENT 4.3-5-2**] However, when a chemical hazard is present in multiple foods, the users of iRISK will only be able to generate exposure, risk, and public health burden estimates for each individual food and users can only relatively rank the public health burden of the foods with this specific contaminant and other pathogen-food pairs. The ranking of hazard-food pairs cannot provide insight into the total public health burden that could be the result from such chemical contamination (in multiple foods), since estimated aggregate exposure and overall public health burden due to a chemical hazard's presence in the food supply cannot be estimated with the current iRISK 1.0 version. This is an inherent limitation of iRISK.

RESPONSE: We plan to develop multi-food feature for future release of FDA-iRISK.

Longer-Term Action Items:

[**COMMENT 4.3-1-2**] The model requires validation against actual disease data, product recall data or other risk ranking/risk assessment tools. The three case studies provided do not provide sufficient information to allow the validation of the model outputs.

RESPONSE: We plan to develop more case studies, including replicating published risk assessments, as a means for further validation. As described in the response for Comment G-1-21, it would be valuable to obtain data from an outbreak in which the concentration and prevalence in the food at consumption, the total number exposed, and the dose-response model are known to implement these data in an FDA-iRISK scenario and compare the predicted risk with real-world results.

CHARGE QUESTION 5: COMMENTS AND RESPONSES

CHARGE QUESTION 5: *Given that the primary purpose of FDA-iRISK is ranking risk among a number of food-hazard pairs:*

CHARGE QUESTION 5.1: *Is variability adequately characterized in the model? If not, please explain what changes might be considered to improve characterization of variability. Comment on other probability distributions (if any) that might be added as templates to characterize variability for exposure from chemical or microbial hazard.*

Noted Strengths:

[**COMMENT 5.1-1-1**] This is beyond the expertise of the reviewer to comment on.

[**COMMENT 5.1-2-3**] For the purpose of iRISK, the user has a sufficient number of probability distributions to choose from. I don't see the need for adding more.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 5.1-3-2**] I think variability is adequately captured or able to be captured in scenario development for inputs such as consumption, age-groups, body weight, etc.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 5.1-5-1**] Since the data input for exposure and dose are provided by the user, it is difficult to comment on whether variability is adequately characterized. As such, this reviewer interpreted this question as asking if the library of parametric models currently in iRISK adequately address the variability of model input parameters that could be faced by iRISK users. It is this reviewer's opinion that the parametric models in iRISK are adequate.

RESPONSE: FDA thanks this reviewer for their comment.

Short-Term Action Items:

[**COMMENT 5.1-2-1**] See my concern about the chronic disease modelling (3.2, Eq. 31).

RESPONSE: Please see the responses to Comment G-1-7 and Comment 3.2-2-2.

[**COMMENT 5.1-2-2**] From the text on page 24 of the Technical Documentation (Section 3.3), I do not understand how the LADD is calculated, and I cannot judge whether the variability is incorporated accurately. It is not clear how the distributions are used. It could help to spell out an example.

RESPONSE: Please see the response to Comment G.2-3.

[**COMMENT 5.1-3-1]** I recommend adding lognormal to the distribution choices for contamination. I was somewhat surprised that a lognormal distribution is not among the options for describing the initial concentration conditions. This is a commonly used distribution for contamination of environmental media[5]. Perhaps lognormal is not commonly observed in food contamination. Even so, presumably iRISK could be used for a water contamination scenario and lognormal could be the preferred choice in that situation.

> **RESPONSE:** The lognormal distribution will be added as an option in the next version of the tool.

Longer-Term Action Items:

[**COMMENT 5.1-4-1**] Characterization of variability associated with exposures to chemical and microbial hazards appears to be one of the weaker aspects of the current iRISK modeling system; substantial additions and enhancements should be considered for incorporation in upcoming versions of the system.

> **RESPONSE:** We will consider further enhancing FDA-iRISK capacity in quantitative treatment of uncertainty for inclusion in upcoming versions of the tool. We would note that FDA-iRISK currently does provide a number of distributions for modeling of variability in the process model and consumption model, and plan to further develop its capacity in describing variability such as adding a multi-food feature and more distribution options for the process model.

[**COMMENT 5.1-4-2**] The two critical elements of the "exposure component" in iRISK, i.e., the Consumption Model and the Population Model offer limited pre-structured options (as opposed, for example, to the options offered in dose-response models). Successful treatment of these two elements would require extensive expertise (and diligence) on the user side. The answer to Question 3.3 above discussed the poor selection of inputs representing variability in amount consumed and in population attributes (specifically the weight distribution for each population group representing a particular life stage). On both elements there is a wealth of public information available, both for the U.S. and internationally; a most accessible summary of information for exposure related factors (mostly U.S.-relevant) can be found in the two *USEPA Exposure Factor Handbooks (for children and for the general population).*

> **RESPONSE:** As described in response to a similar comment under Question 3.3, examples in the peer review workbook were intended to function only as illustrations of the use of the tool and so the inputs listed may not necessarily provide faithful representations of the risk. We concur with the reviewer that daily consumption may vary, and body weight may not follow a uniform distribution. The scenarios may be revised in future releases. FDA-iRISK is intended for international use as well as for use in the United States. As such, no assumption is made as to the appropriateness of any specific source of exposure or consumption data; this requires the user's evaluation. The FDA-iRISK tool is available

[5] See Chapter 4 in Cullen AC and HC Frey. Probabilistic Techniques in Exposure Assessment. New York: Plenum Press, 1999.

through the JIFSAN-hosted site (www.foodrisk.org) which provides multiple sources of (or links to) information of the type identified by the reviewer (e.g. links to resources such as the EFSA Comprehensive European Food Consumption Database as well as many of the US databases from which the tables in the USEPA Exposure Factor Handbook were derived). This resource can be continually updated independently of FDA-iRISK for multiple uses, while being convenient to users of FDA-iRISK.

[**COMMENT 5.1-4-3**] Empirical distributions for various exposure factors relevant to the U.S. population (by gender and age) can be readily derived from the tables in those Handbooks and *it is strongly recommended that upcoming versions of iRISK develop and incorporate such distributions as "built-in" options for the user.* There are numerous other works that provide valuable—and easily accessible—information on distributions that "capture" variability in exposure-relevant parameters; examples are:

- EFSA. 2006. Guidance Related to Uncertainties in Dietary Exposure;
- European Commission. 2002. Risk Assessment of Food Borne Bacterial Pathogens: Quantitative Methodology Relevant for Human Exposure Assessment;
- IPCS/WHO. 2008. Uncertainty and Data Quality in Exposure Assessment;
- IPCS/WHO. 2009. Dietary Exposure Assessment of Chemicals in Food. Chapter in Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food.

Another standard and extremely valuable source on forms and attributes of probability distributions for exposure assessments is the monograph:

- Cullen, A.C., and Frey, H.C. 1999. Probabilistic Techniques in Exposure Assessment: A Handbook for Dealing with Variability and Uncertainty in Models and Inputs. New York: Plenum Press.

Future versions of iRISK would benefit substantially by incorporating characterizations of variabilities in exposure factors that are available in the above mentioned resources.

RESPONSE: Please see the response to Comment G-4-10. We recognize a need for guidance and training associated with using FDA-iRISK, and will consider providing the references suggested by the reviewer as a resource for users. We will also evaluate and as appropriate develop additional case studies, taking into consideration the reviewer's suggestions.

[**COMMENT 5.1-5-2**] For some parameters, such as food intake, custom distribution (empirical) should also be allowed.

RESPONSE: The cumulative empirical distribution is available in version 1.0 of FDA-iRISK and is intended for entering custom distributions.

CHARGE QUESTION 5*: Given that the primary purpose of FDA-iRISK is ranking risk among a number of food-hazard pairs:*

CHARGE QUESTION 5.2: *Comment on the appropriateness and adequacy of how consumption is defined for acute versus chronic chemical exposure. Considering how consumption is defined for chronic chemical exposure, to what extent (if any) the exposure might be over or underestimated? If so, the reviewer should explain what changes might be considered to improve the consumption estimate to be more consistent with current modeling practices in which estimates of risk are generated while balancing the need for broad risk ranking using the annual DALY.*

Noted Strengths:

[**COMMENT 5.2-2-1**] This question is typical for chemical exposure and risk, and not my expertise.

[**COMMENT 5.2-3-3**] I think the options within the iRISK system will allow for consistent and comparable consumption estimates to be developed.

> **RESPONSE:** FDA thanks this reviewer for their comment.

Short-Term Action Items:

[**COMMENT 5.2-3-2**] There is a variety of consumption modeling approaches in current use; the ones I am familiar with have built-in databases populated with individual food intakes from the CSFII and/or NHANES/WWEA. Long-term consumption is then modeled drawing on the individual food intake data. I am not very familiar with the Total Diet Study so I don't know how it compares to the other surveys as far as overall confidence in characterizing food intakes for any particular food. Depending on the circumstances of any particular food and risk scenario, using data from one of the available surveys may be preferable. This is why documenting data inputs, including describing the strengths and limitations of particular data sources, is important for risk models that support decision making.

> **RESPONSE:** FDA thanks this reviewer for their comment and agrees that documenting data inputs is important for risk models that support decision making. FDA-iRISK provides the "Notes" feature to allow users to document inputs.

[**COMMENT 5.2-4-1**] As mentioned in multiple instances within the answers to previous questions (for example, see answer to Question 3.1), the relationship of acute and chronic exposures considered by iRISK needs substantial clarification.

> **RESPONSE:** The Technical Documentation has been revised and a section added on risk estimates generated by FDA-iRISK. This section discusses the relationship of acute and

chronic exposures considered by FDA-iRISK. We plan to make the revised Technical Documentation available.

[**COMMENT 5.2-5-2**] Also, as noted earlier, the mean *per user* food intake is used in iRISK to derive the LADD for cancer risk assessment. This could be an overestimate of chronic usual intake when dealing with infrequently consumed foods.

RESPONSE: We agree with the reviewer's assessment regarding the potential for overestimating consumption in this case. We believe that the reviewer identifies a generic challenge associated with inferring chronic consumption from short term consumption surveys such as 2-day surveys. Use of FDA-iRISK does not differ from other approaches to chemical risk assessment in facing this challenge. Also of note, the user is not restricted to using the mean *per user* food intake; *per capita* food intake may be used where appropriate.

Longer-Term Action Items:

[**COMMENT 5.2-1-1**] For the acute model, consumption is eating occasions per year for the population, and amount eaten per occasion (single value or distribution). Consumption for the chronic exposure model is defined as the number of consumers and the associated population groups. The user then inputs the average daily consumption (as a fixed value or a distribution) in units of mass per day (body weight of the age group is also taken into account).

The factors which could affect the estimate of consumption include the size of the population, the age groups eating the food, the body weight, and the amount of food consumed per day. Assuming that the body weight and the population are fixed (except for some specific foods such as infant cereals) for all entries, the age groups and the amount of food per day would be the most important variables. The estimate has to be based on either typical consumers or high-end consumers, and at what age(s) the food is commonly consumed. This information could be based on surveys of the eating patterns of the population or market availability versus population.

The model currently assumes a typical consumer. Additionally, looking at high end consumers or special populations would be helpful.

RESPONSE: The user of FDA-iRISK defines the consumer and the consumption pattern. As such, the daily consumption amount for a specific scenario can be defined so that it represents a typical consumer, a high end consumer, or a special population, provided that consumption is known. Alternatively, by using a distribution, a range of daily amounts representing a range of consumption levels within the cohort can be described.

[**COMMENT 5.2-3-1**] I can't address the question of over- or underestimation. I think knowledge of chronic consumption is very limited—it is an important uncertainty in food consumption modeling. Additional research is probably needed to truly understand whether any particular modeling approach over- or underestimates chronic consumption.

RESPONSE: We agree that the estimation of chronic consumption over a lifetime is a particularly challenging issue.

[**COMMENT 5.2-3-4**] iRISK models age-specific populations using distributions for food intake and body weight. If these age-specific population inputs are derived from the same source data (CSFII or NHANES), model comparability is likely to be good. Some considerations for defining consumption:

- Take account of non-consumers;
- Develop consistent age-specific groups; and
- Define more age groups, i.e., 2-3 year groupings rather than 5-year or larger groupings.

RESPONSE: In defining the consumption model, the user specifies the number of consumers, which need not be the entire population (this would take into account non-consumers). The user also specifies the specific age range represented by each group, and depending on the purpose of the risk assessment, users could identify or obtain some consensus on an acceptable standard on age-grouping for many foods. The resolution of the age-strata could be selected in accordance with the availability of data and we agree that, where appropriate, consistent age-grouping is desirable, as is consideration of non-consumers.

[**COMMENT 5.2-4-2**] Current ("state-of-the-art") modeling practices employ "bottom-up" approaches that "build" distributions representing intra-individual variability over time for chronic exposures simultaneously with inter-individual variability within a population by considering stochastic ensembles of "exposure events" involving "virtual individuals" sampled from the population of concern. Such approaches are computationally intensive and maximize the use of available databases on population physiology, demographics, and behavior (including consumption patterns), etc. (e.g., NHANES, CHAD, CSFII, etc.) to allow the development of detailed associations of exposure and risk outcomes with various biological and socioeconomic factors. Of course, such approaches may not be appropriate for incorporation into a model intended for "routine use" of simplified case studies, such as iRISK;

RESPONSE: We agree with the reviewer that greater precision may be obtained by modeling intra- and inter-individual variability. FDA-iRISK is designed to assist practitioners needing to prepare relatively rapid, fully documented, consistent risk assessments of several or a large number of food-hazard combinations in order to rank the estimated public health impact. In situations where assessors elect to develop more complex, computational intensive assessments than are currently available in FDA-iRISK, the results of these assessments can be included in FDA-iRISK rankings using the "specified" type of risk scenario.

[**COMMENT 5.2-4-3**] … however, comprehensive models can be used in a comparative "benchmarking" setting to test how iRISK-based calculations can replicate aspects of the detailed simulations from these models. For example, the new SHEDS-Dietary model of USEPA (Xue et al., 2012) could be used to develop and run well-defined simulations, for both acute and chronic exposures, and then test-runs can determine what features of the detailed simulations can be replicated, and to what extent, with iRISK. The rationale for such a study is to use the results

of the detailed simulations as "proxy" to real measurements (since detailed measurements do not really exist) and to compare patterns within the detailed results to those that could be derived through iRISK as a means of evaluating how well the simplified model (e.g., iRISK) can reproduce the behavior of the comprehensive model (e.g., SHEDS). Since the behavior of the comprehensive model is supposed to be governed by less restrictive assumptions and be informed by more details relevant to the real world system, comparative testing of the two models will provide valuable insights into the nature and the impact of the limitations inherent in the simpler model.

> **RESPONSE:** FDA is in the process of comparing the results of detailed risk assessments with those produced by FDA-iRISK for a select number of microbial and chemical hazards. These comparisons contribute to the identification of which FDA-iRISK options (e.g. distribution choices) are most useful for replicating the results of the more elaborate models and may also suggest new features for development.

[**COMMENT 5.2-5-1**] As noted earlier, in iRISK, an acute exposure to a hazard is considered to refer to exposure during a single eating occasion (EO). While this single bolus dose scenario is possible (i.e., acute poisoning event), in chemical exposure and risk assessment, the short term exposure of interest could also be in the form of a single day or a weekly exposure. iRISK should allow for input of short term exposures other than the g/EO, such as dose calculated based on a 24-hr intake. These daily intake estimates should be higher than the LADD calculated under the chronic exposure but below the bolus dose of g/EO.

> **RESPONSE:** Please see the response to Comment 3.1-5-1.

CHARGE QUESTION 6: COMMENTS AND RESPONSES

CHARGE QUESTION 6: *The FDA-iRISK Monte Carlo simulation is designed to address variability, and uncertainty can be explored by scenario analysis. Given the practical constraints of the model and data, a sensitivity analysis option will be provided by which the user can change parameters or distributions in the model inputs and obtain ranked results as compared to the original scenario. If this approach is not sufficient, please provide additional or alternative approaches and explain what changes might be considered and how they would improve the model.*

Noted Strengths:

[**COMMENT 6-1-1**] This is beyond the knowledge and expertise of the reviewer to comment on.

[**COMMENT 6-5-1**] The above approach is sufficient.

RESPONSE: FDA thanks this reviewer for their comments.

Short-Term Action Items:

[**COMMENT 6-4-4**] It should also be mentioned that, in 2006 and 2007, the Scientific Committee of the European Food Safety Authority (EFSA) developed guidance for treating uncertainties in chronic and acute dietary exposure assessments (EFSA, 2006 and 2007). In 2008, guidance was developed also by a working group of the International Program on Chemical Safety (WHO, 2008). The framework proposed by EFSA and WHO considers a progression from simpler uncertainty analyses to more complex tiers of uncertainty analyses. Tier 0 consists of a point estimate derived with conservative assumptions and default values. Tier 1 consists of a point estimate that is more refined and an indicative range for the associated uncertainty is given. Tier 2 considers multiple point estimates based on different combinations of assumptions; the uncertainty in the point estimates can still not be quantified. Higher tiers require full probabilistic dietary exposure assessments.

RESPONSE: FDA thanks this reviewer for their comment and will consider the suggested material when revising the uncertainty analysis features of FDA-iRISK in future releases.

Longer-Term Action Items:

[**COMMENT 6-2-1**] In larger microbial risk assessment models, the common approach is indeed to address the variability (which determines the risk) and explore the impact of the uncertainty (which is difficult to characterize) by scenario analyses. There is, to my knowledge, no easy alternative to that.

One can wonder how the uncertainty impacts the risk ranking. Ideally, one would like to identify "significant" differences in ranking, but it will be difficult to do that by scenario analyses only. In that case, the scenario analyses must be systematic, but that will be quite a challenge, as the "best solution" will very much depend on the specific case. Still, it would be nice if iRISK provides "uncertainty intervals" of the risk ranking scenarios for the same case, so the user gets some insight in how significant the differences in ranking between different hazard/food combinations are.

> **RESPONSE:** FDA thanks this reviewer for their comment and will consider this suggestion when revising the uncertainty analysis features of FDA-iRISK in future releases.

[**COMMENT 6-3-1**] I think a scenario analysis utility will be very useful. I do not know how more sophisticated uncertainty analysis could be incorporated into the structure of iRISK.

> **RESPONSE:** FDA thanks this reviewer for their comment.

[**COMMENT 6-4-1**] Scenario-based sensitivity analysis cannot adequately address the multiple uncertainties; a *two-stage (or two-dimensional) Monte Carlo analysis* would be the proper approach for treating both variability and uncertainty for a given exposure/risk scenario. Monte Carlo analysis is challenging for models containing a large number of variables that are associated with variabilities and uncertainties. Available USEPA guidance describes the "principles of good practice" for the conduct of Monte Carlo simulations (USEPA, 1997) and these should be recommended for current and future applications of FDA-iRISK.

> **RESPONSE:** FDA thanks this reviewer for their comment and will consider the suggested material when revising the uncertainty analysis features of FDA-iRISK in future releases.

[**COMMENT 6-4-2**] As an interim alternative, and as per standard guidance for other types of models (see, e.g., USEPA 2009 *Guidance on the Development, Evaluation, and Application of Environmental Models*), one-at-a-time (OAT) sensitivity analyses are useful. The procedure involved is to choose a base case of input values and to perturb each input variable by a given percentage away from the base value while holding all other input variables constant. Most OAT sensitivity analysis methods yield local measures of sensitivity that depend on the choice of base case values. To avoid this bias, Saltelli et al. (2000) recommend using a method called "Morris's OAT" for screening purposes because it is essentially a global sensitivity analysis method that involves computing a number of local measures (randomly extracted across the input space) and then taking their average. Morris's OAT provides a measure of the importance of an input factor in generating output variation, and while it does not quantify interaction effects, it does provide an indication of the presence of interaction.

> **RESPONSE:** FDA thanks this reviewer for their comment and will consider the suggested material when revising the uncertainty analysis features of FDA-iRISK in future releases.

[**COMMENT 6-4-3**] It should be kept in mind that there are multiple of sources of uncertainty in exposure assessment (e.g., chemical analysis of food products, biased sampling, food consumption surveys, number and size of meal portions, composition of the sample ingredient percentages in recipes) and the uncertainties can be large. Analysis of both inter-individual and intra-individual (over a time period) variabilities and uncertainties is required to enable a proper interpretation of the outcome of an exposure assessment. Therefore, a thorough two-dimensional variability-uncertainty analysis can aid policy makers in taking decisions with respect to dietary exposure to substances.

> **RESPONSE:** FDA thanks this reviewer for their comment and will consider the comment when revising the uncertainty analysis features of FDA-iRISK in future releases.

CHARGE QUESTION 7: COMMENTS AND RESPONSES

CHARGE QUESTION 7: *Comment on the FDA-iRISK user interface. Is the interface user friendly? Are there any features that should be modified or added to facilitate ease of use? For example, is there sufficient description in the user interface to understand each component of the model?*

Noted Strengths:

[**COMMENT 7-1-1**] The user interface is user-friendly and provides an enormous degree of flexibility to the user.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 7-2-3**] (3) I like the sharing option and the placeholder process type. These can be very helpful in practice.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 7-3-1**] I found the interface to be easy to use—thinking about any particular page or tab. I found the text was clear and understandable. There are many aspects to developing a complete scenario and the tabs help keep things organized for each part of the model.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 7-5-1**] Yes, the interface is user friendly. It is easy to follow and use.

RESPONSE: FDA thanks this reviewer for their comment.

Short-Term Action Items:

[**COMMENT 7-1-2**] The inclusion of pictograms of the dose-response curves and the prevalence might be more helpful than text-based listings (faster and easier to select).

RESPONSE: FDA will consider this suggestion for future releases.

[**COMMENT 7-2-1**] (1) The user needs some time to learn how iRISK works, and needs some experience before (s)he can work with iRISK. Guidance, like given in the workbook, is very useful for this purpose. After being involved in some reviews of iRISK, I have some experience by now, and find my way into the system quite easily. It is a bit of a struggle to find your way through defining food, hazard, process models and risk scenarios, and to be sure you have defined everything at the right moment and in the right order. (From hazard down to metric, then from food down to consumption models, then the process model and then the scenario, you are not well guided through that process by iRISK). On the other hand, you cannot really blame the developers of iRISK that the user may have a "quick and dirty" mind.

RESPONSE: FDA will consider options to streamline the user experience for future releases.

[**COMMENT 7-3-2**] However, as a new user, I find it hard to remember exactly where any particular data input is. There is a slide on page 13 of the workshop handout (Database Structure for Scenarios) that could be included in the Technical Documentation and/or the training workbook that might help keep new users oriented.

RESPONSE: FDA will consider improvements to the navigation and documentation to make it easier to locate specific elements.

[**COMMENT 7-4-2**] Obviously, there are numerous inefficiencies and potentially confusing issues associated with the above "schema." For example, the tab for Process Models appears at two successive hierarchical levels, i.e., "existing" at the same level as Hazards, Foods, and Risk Scenarios, as well as at a lower level, once grouped with Dose Response, Metrics, Process Models, Scenarios, once grouped with Consumption Models, and Scenarios. To many users, it would not be clear (at least without further investigation) that tabs at different levels would provide access and control to the same type of information.

Tabs for Scenarios or Risk Scenarios appear to co-exist with tabs at all "levels" of the system. To access and define one of the independent/primary essential elements of the risk paradigm, i.e., the potentially exposed Population, the user has to "navigate" first from Models to Foods to Consumption Models before she/he is given such access; this is *not* an example of efficient and intuitive interface design.

RESPONSE: FDA will consider options to streamline the user experience for future releases.

[**COMMENT 7-4-4**] Some supplementary recommendations for enhancing/improving the user interface follow:

It would be useful (especially for new users) for each tab to provide a hypertext link containing relevant definitions and explanations of the terms in that tab. This could be access to items in an online glossary clarifying the usage terms that may be ambiguous to new users or have different meanings in different fields (e.g., prevalence, process model, etc. could have different meanings for a statistician, a food scientist, and an engineer).

RESPONSE: The next version of FDA-iRISK will move instructions to a dedicated tab which will provide additional space to provide guidance on each element. Guidance on each element will be expanded in future releases.

[**COMMENT 7-4-5**] …It would be helpful to have a schematic or a table as permanent element on the user screen, listing elements for which information needs to be provided and showing a corresponding check mark once the relevant information is filled. That would ensure that one does not miss critical information before one goes to the report generation step. For example, in the current format, one can add Food, Hazard, and Consumption information and ask for report generation only to find an error saying that Population Groups are not defined.

RESPONSE: FDA will consider options to streamline the user experience for future releases.

[**COMMENT 7-4-6**] …Report generation should provide more options for organizing report information, for selecting portrait or landscape options and adding structured bookmarks to the PDF file, etc.

RESPONSE: FDA will consider these reporting enhancements for future releases.

[**COMMENT 7-5-2**] The terminology "hazard metric" for the hazard module is a bit confusing. This metric is really about the health burden so it should reflect that. The terms "health burden" or "public health burden" metric are suggested to be used in place of hazard metric.

RESPONSE: The term Hazard Metric will be changed to Health Metric in future releases.

Longer-Term Action Items:

[**COMMENT 7-2-2**] (2) When working with iRISK, I tried to apply the same population group (e.g., consumers of chicken meat: a specific number of consumers eating specified portions, different age groups) for an acute and a chronic risk (so with very different dose response models). I did not see a possibility to use the population group twice. It seems that you have to define it twice in such a case, which is a little cumbersome. Specifically for risk ranking (in this specific population group of chicken meat consumers), it seems obvious to compare different hazards for the same population group. I would either like the possibility to use a population group twice for the same food product or (if it is actually possible to do this, but I just didn't see how to do it) a better guidance in doing it. The problem is, I think, that the population group is defined under the consumption model (which is defined for the exposure type), and you cannot copy and paste population groups to new consumption models.

RESPONSE: The current structure of the consumption models and population groups in FDA-iRISK reflects a trade-off between flexibility and the reuse of consumption models and their associated population groups. FDA will consider this comment and review the current implementation for possible modification in future releases.

[**COMMENT 7-4-1**] The user interface of FDA-iRISK employs a "tab-based" model (that traditionally is intended to derive from and conceptually refer to traditional "physical" filing systems) and is easy for the user to navigate; however, it is certainly not optimal, and can be confusing at times, as it does not adhere systematically to a standard hierarchical model, reflecting the essential elements and the modeling procedures of the modeling system. Indeed, as discussed earlier, iRISK considers seven essential elements of the risk assessment system, i.e., three independent/primary elements (Hazards, Foods, Population Groups) and four dependent/derived elements (Food Production and Process Models, which depend on both the Foods and the Hazards; Consumption Models, which depend on both the Foods and the Population Groups; Dose Response Models, which depend on both the Hazards and the

Population Groups and are "informed" by the Process Models and Consumption Models; and Health Metrics, which depend on the Dose Response Models and the Population Groups). These seven elements should be at the same hierarchical level of model organization, and their corresponding "interface tabs" should appear together (and be always available on the screen for easy user access). Instead, in the iRISK interface, the situation is currently as follows:

The "top" (fixed) set of tabs on the user screen are: Home, Models, Reports, Sharing, Help; these are always available to the user.

- When the tab for Models is selected, the working set of tabs is: Hazards, Foods, Process Models, Risk Scenarios.
    - When a specific Hazard is selected under Models, the working set of tabs becomes: Name and Type, Dose Response, Metrics, Process Models, Scenarios, Notes, providing access to, and the opportunity to define/edit Dose Response models, Process Models, and Health Metrics.
    - When a specific Food is selected under Models, the working set of tabs becomes: Name and Type, Consumption Models, Process Models, Scenarios, Notes.
        - When a specific Consumption Model is selected under Foods, the working set of tabs becomes: Name and Parameters, Population Groups, Scenarios, Notes, providing—only then—access to, and the opportunity to define/edit attributes of the Population of concern.

RESPONSE: The current interface structure represents a tradeoff between grouping related items and providing direct access to all model elements. FDA will consider this comment and review the current implementation for possible modification in future releases.

[**COMMENT 7-4-3**] Based on the above discussion, *it is strongly recommended* that, when the Models tab is selected from the "top level row of tabs" (Home, Models, Reports, Sharing, Help), a "second level row of tabs" should appear, corresponding to the seven essential elements of the FDA-iRISK modeling system (Hazards, Foods, Population Groups and Process Models, Consumption Models, Dose Response Models, Health Metrics), and that this row should remain available as long as Models is selected. A separate tab (ideally at a separate location on the user screen, rather than grouped with the other tabs of different levels) should offer access to Scenarios at all levels.

RESPONSE: The current interface structure represents a trade-off between grouping related items and providing direct access to all model elements. FDA will consider this comment and review the current implementation for possible modification in future releases.

[**COMMENT 7-4-7**] User input under "Add Hazard" and "Add Foods" could be facilitated by adding "drop-down selection menus" that include "user-defined text input box." Drop-down menus listing common hazards or food items would be especially helpful if information (relevant parameterizations, distributions, etc.) that is specific to these items is incorporated into the modeling system in future versions of iRISK.

RESPONSE: At this time, all input remains the responsibility of the user. We believe examples for parameterizations and distributions would be better illustrated through case studies (e.g. Chen et al. 2013) and potentially through more examples in the User's Guide. We plan to evaluate the feasibility to provide a feature in FDA-iRISK to define and save their own default values or parameters.

CHARGE QUESTION 8: COMMENTS AND RESPONSES

CHARGE QUESTION 8: *Comment on the adequacy of the model documentation features within FDA-iRISK. Can the user accurately document data sources and confidence in the model?*

Noted Strengths:

[**COMMENT 8-1-1**] The user has a lot of flexibility in terms of recording sources of information in a text format. This presumably could include references to papers, websites, and other sources of information. The user has free rein in terms of recording assumptions, limitations and uncertainties associated with inputs or outputs. I also like the ability to share or hide notes.

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 8-2-1**] I really like the report structure, and the fact that you can so easily get a (more or less detailed) report of your model. There are plenty of possibilities for notes, so my answer on the question is "yes."

RESPONSE: FDA thanks this reviewer for their comment.

[**COMMENT 8-4-1**] The model documentation features are useful and, depending on the expertise (and the diligence) of the user, could add substantial value to any application of the iRISK modeling system.

RESPONSE: FDA thanks this reviewer for their comment.

Short-Term Action Items:

[**COMMENT 8-2-2**] I do, however, miss a description of the exposure assessment; the distribution of doses/final concentration in the servings or distributions of unit sizes and prevalences (if these exist). You may not need that for risk ranking, but it would enhance my possibilities for quality control of my own model, and simply increase my understanding of what the model is doing. Not all users want this, but if you want it, you should have the option to get this information. Actually, I would like to have the opportunity to get a description of the distributions at every process step (as percentiles or in graphs).

RESPONSE: FDA is considering options to provide additional intermediate results for advanced users of FDA-iRISK in future releases.

[**COMMENT 8-4-2**] However, providing/facilitating options for more "structured" and complete documentation would greatly improve these documentation features.

RESPONSE: FDA will consider enhancing the documentation features of FDA-iRISK in future releases.

Longer-Term Action Items:

[**COMMENT 8-1-2**] This user would appreciate the ability to link or to import Excel-based data or graphs, particularly to document exposure data.

> **RESPONSE:** FDA will consider enhancing the documentation features of FDA-iRISK in future releases to include linkage to or the attachment of documents such as Excel spreadsheets.

[**COMMENT 8-3-1**] The notes utility is adequate to document risk scenarios, but whether users do it and do it well is an open question. Two thoughts on this:

1) Add instructions on each Note page to prompt users to document data sources and uncertainties related to that step of model development whether it is data inputs or dose-response model choices, etc.
2) Risk assessments used for decision making must be thoroughly documented – consider 'forcing' the notes function—or making the user opt-out of keeping notes when developing a particular scenario.

RESPONSE: FDA will consider adding more prompts or additional features in future releases to encourage users to document data sources and assumptions. We do not plan at this time to require users to either opt-out or opt-in of notes.

[**COMMENT 8-4-3**] For example, it would be very useful if the web interface for user documentation offered: Multiple "drop-down selection menu lists" (including the option other or user defined text) of major options for different elements of the documentation. These lists would not only facilitate report preparation for all users; they would provide guidance to new users (and help organize their work).

> **RESPONSE:** FDA will consider adding a "note" type dropdown list which users could use to assign types to their notes (e.g. reference, rationale) in future releases. We will also consider the option of providing a centralized location where users can review all their notes, grouped by element type (e.g. hazard).

[**COMMENT 8-4-4**] For example, it would be very useful if the web interface for user documentation offered: …Options to access and store links to public bibliographic databases (such as PubMed) from within the FDA-iRISK system, allowing users to easily document sources of data and other information used in developing iRISK Scenarios, in selecting and parameterizing iRISK component models and variability distributions, etc.

> **RESPONSE:** FDA will consider enhancements to the note option that allow links to external references in future releases.

[**COMMENT 8-5-1**] This model documentation is currently in the note format in iRISK, which appears to be optional and not required to be filled out by users. It is recommended that users be required to complete this field with the following mandatory information: 1) peer-review status

of data; 2) data sources and reference; and 3) user's confidence in data. The tool should be set so that users cannot move on to the next step without the required information completed.

RESPONSE: At this time, FDA relies on individual users and their organizations to establish guidelines on the level of documentation required. FDA will consider options to facilitate this process in future releases.

OTHER SPECIFIC OBSERVATIONS

Reviewer #1

SPECIFIC OBSERVATIONS ON THE TECHNICAL DOCUMENT

Page	Line	Comment
1	11,17, 23, 27	What is section 0, which is supposed to provide information on the burden of disease? **RESPONSE:** The reference to Section 0 is a typo and has been corrected in the revised Technical Documentation 1.0. We have posted the revision at https://irisk.foodrisk.org/Documents/FDA-iRISK10TechnicalDocumentation.pdf.
2	9	What is section 0, which is supposed to provide information on the burden of disease? **RESPONSE:** The reference to Section 0 is a typo and has been corrected (see revision at https://irisk.foodrisk.org/Documents/FDA-iRISK10TechnicalDocumentation.pdf).
Multiple	-	P is used for both prevalence and probability – please distinguish and treat each dose-response model separately and explain variables. **RESPONSE:** We will address this issue in future revisions of the Technical Documentation.
Multiple	-	S is defined in the overview but is never referred to again in the document, at least not as an equation. **RESPONSE:** This will be addressed in the revised Technical Documentation.
Multiple	-	The order information is presented in the technical documentation is not the same as the order that one would input information into the model; consider some way of better linking the technical information and the tool. **RESPONSE:** Please see the response to Comment G-5-7.

SPECIFIC OBSERVATIONS ON THE iRISK MODEL

[This reviewer did not provide any specific comments on the FDA-iRISK model.]

Reviewer #2

SPECIFIC OBSERVATIONS ON THE TECHNICAL DOCUMENT

Page	Line	Comment
1	-	There is no Section 0 (last bullet). **RESPONSE:** The reference to Section 0 is a typo and has been corrected (see revision at https://irisk.foodrisk.org/Documents/FDA-iRISK10TechnicalDocumentation.pdf).
3	-	Prevalence "may be a distribution." I don't understand how this prevalence can ever become a distribution, as it is a statistic of the population. If it has a distribution, I don't know how to interpret it. It can only be a distribution if: a) Several food lots are compared (but I don't see where this can be included in the model, or how these would be defined; it would also imply a more-dimensional distribution of concentrations). b) It expresses uncertainty, but this is not modeled (??) c) It is a distribution of the probabilities that each sampled food unit has zero concentration. That is not an informative quantity. The only interesting quantity is the probability that a random food unit has a concentration zero, which is the mean of that probability distribution (i.e., the distribution of the probabilities that each sampled food unit has zero concentration). So I assume the "may be a distribution" is wrong (but see my reply to Charge Question 3.3). In that case, the report should not refer to mean prevalence but to prevalence, as there is no distribution to take a mean of (see my reply to Charge Question 8). If the prevalence can be a distribution, this issue should be well explained in the Technical Documentation. **RESPONSE:** When applied to the results of process stages, the term "prevalence" refers to the probability of contamination of a unit of food for a given iteration. Because this value can be different on each iteration, we referred to it as being distributed. The Technical Documentation has been revised to make this more explicit and we plan to make the revised document available. We plan to develop an example in the future to illustrate how probability of contamination is calculated.
4	-	0.001 cfu should be 0.01 cfu. **RESPONSE:** This is a typo and has been corrected in the revised

Page	Line	Comment
		Technical Documentation.
8	-	The positive binomial function is not given in that chapter. **RESPONSE:** We plan to provide more description of this function in future revisions of the Technical Documentation.
21	-	I would use "serving" instead of eating occasion throughout the document. **RESPONSE:** The term "eating occasion" is used instead of "serving" to account for times when an individual may consume several servings during a single eating occasion (e.g. 2 hamburgers). We will provide additional explanation of the term in future versions of the Technical Documentation and/or User Guide.
21	-	Reference to Fig 2 gives an error message. **RESPONSE:** This has be addressed in the revised document.
38	-	Section 0 should be 4.4. **RESPONSE:** This has been corrected (see revision at https://irisk.foodrisk.org/Documents/FDA-iRISK10TechnicalDocumentation.pdf).

SPECIFIC OBSERVATIONS ON THE iRISK MODEL

URL/Steps to get to URL	Comments
https://irisk.foodrisk.org/Tool/EditHazardMetric.aspx?	In the edit hazard metric box, you can either give a value for the DALY, or compute it. There is no unit given; I guess it is DALY per case in years. You might consider given a warning if one gives a number > 100 or so. **RESPONSE:** The unit is DALY. FDA is reviewing all inputs for possible additional validation in future releases.
https://irisk.foodrisk.org/Tool/EditProcessModel.aspx?ProcessModelGUID	In the edit process model, one can indicate that the initial concentration is 10 kg/g. A warning may be appropriate. **RESPONSE:** FDA will consider additional validation for future releases to alert users in this situation.
Edit process stage, process type pooling - chemical	The new unit size should be larger than it was, but the value of what it was is not given, so the user should remember it. If I make it smaller than it was, I get no error message.

URL/Steps to get to URL	Comments
	RESPONSE: FDA is reviewing all inputs for possible additional validation in future releases.
Edit process stage, process type partitioning - chemical	Here, you can add a larger unit size. I thought partitioning meant splitting up, here it is just a change in unit size, it seems. This should not be possible, or the process should be renamed. **RESPONSE:** FDA is reviewing all inputs for possible additional validation in future releases.

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