U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

FDA's Response to External Letter Peer Review [1] of "FDA-iRISK® 5.1 Advanced Modeling Features and Technical Document (March 2025)"

July 2026

[1] "Report: External Letter Peer Review of FDA's FDA-iRISK® 5.1 Advanced Modeling Features and Technical Document." Versar Global Solutions, March 4, 2025.

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I. INTRODUCTION

FDA-iRISK® is a web-based, interactive risk assessment tool developed by the Human Foods Program in the U.S. Food and Drug Administration (FDA). This food safety modeling tool enables users to conduct quantitative analyses on a wide range of food safety hazards, rank risks from both microbial and chemical hazards in foods, and compare the effectiveness of prevention and control measures, expressed as public-health metrics. Risk managers and other stakeholders can use FDA-iRISK to inform food safety priorities and risk management decisions.

FDA-iRISK has many built-in functions and automated features that allow users to conduct fully quantitative, fully probabilistic risk assessments relatively rapidly and efficiently. This peer-reviewed tool enables users to enter data and create scenarios that mathematically simulate food-hazard combinations and conditions at any point in the food chain, through to consumption, to reflect real-world food safety issues. FDA-iRISK provides a modeling framework with foundational features that enable users to explicitly assess and separate the effects of variability from those of uncertainty by probabilistic second-order Monte Carlo simulation. Since the initial launch of FDA-iRISK, in 2012, FDA has continued to expand the tool's capacity. Previously FDA conducted several technical reviews (peer reviews) as new features had been developed. Comments from the technical reviewers were used to inform development and refinement of the FDA-iRISK system, which resulted in the release of FDA-iRISK 4.2 in March 2021. In recent years, FDA further developed a number of new features, which were included in the FDA-iRISK institutional version 5.1 that also serves as a development platform before new features are released in the FDA-iRISK public version.

FDA contracted with Versar Global Solutions (Versar), an independent FDA contractor that coordinated an external letter peer review of FDA-iRISK 5.1 (aka FDA-iRISK 5.1i) advanced modeling features (new features) and technical documents. Versar conducted an independent search and identified three scientific experts where one reviewer has chemical risk assessment expertise, and two reviewers have microbial risk assessment expertise.

Peer Reviewers and Affiliations:

Maarten J. Nauta, PhD, Statens Serum Institut, Denmark
Nga Tran, Dr. PH, MPH, Exponent, Washington, DC
Donald W. Schaffner, PhD, Rutgers University, New Brunswick, New Jersey

This report describes FDA's response to comments and suggestions made by the reviewers, including how FDA has developed and refined features, and made updates available in FDA-iRISK 5.0, the public version released in March 2026 (available at https://irisk.foodrisk.org). The report also describes considerations for future enhancements of the FDA-iRISK system in response to the peer review comments that we have compiled and summarized here in.

II. CHARGE TO REVIEWERS

FDA-iRISK® is a web-based tool for modeling food safety risks and interventions. It provides many built-in features and mathematical equations designed to enable users to conduct probabilistic risk assessments relatively rapidly and efficiently, including complex models with second-order Monte Carlo simulation. Previously FDA conducted technical reviews as new features had been developed. Comments from the technical reviewers have been used to inform further development and refinement of the FDA-iRISK system. Since the initial launch of FDA-iRISK, in 2012, FDA has continued to expand the tool's capacity.

The focus of this peer review we are now undertaking, in which you are being asked to participate, is on new features (Appendix I) developed for FDA-iRISK 5.1. There are 22 new features organized in four groups: A) features useful for the Process Model, including linkage to ComBase (A1 through A8), and linkage to the FDA-OC App (A9); B) features useful for the Consumption Model; C) features useful for the Risk Scenario; and D) features for enhancing the User Interface Experience. Test cases are provided for most of the new features and, notably, Analytica files are provided for several features including B1, B3, C2 and C5 (highlighted in Appendix I). Where appropriate, the reviewer is encouraged to comment on the adequacy of the new features to model microbial hazards, chemical hazards, or both types of hazards, based on the reviewer's areas of expertise. Reviewers will be provided access to the FDA-iRISK tool, test cases, and other documents.

1. For Group A features, please review the FDA-iRISK tool, test cases, and the methodology (relevant sections) described in the FDA-iRISK 5.1 Technical Document provided.
    a. For features A1 through A7, is the linkage to ComBase adequate to capture the outputs from ComBase (https://combase.errc.ars.usda.gov/) appropriately, and to upload the ComBase results accurately into the FDA-iRISK tool? If not, please explain what changes might be considered to improve the feature(s).
    b. For feature A8, is the rationale provided in the Technical Document appropriate for no longer requiring a temperature distribution when applying imported ComBase models? If not, please explain what changes might be considered.
    c. For feature A9, is the linkage to the FDA-OC App adequate to capture the outputs from the FDA-OC App (https://foodsafetyrisk.org/OC/) appropriately, and to upload the OC curve results accurately into the FDA-iRISK tool? If not, please explain what changes might be considered to improve the feature.

2. For features B1, B3, C2 and C5, please review the associated Analytica files and the methodology (relevant sections) described in the Technical Document. Evaluate whether the new features are adequate according to current modeling and peer-review practices.
    a. Are any of the assumptions associated with the methodologies for these features (including the underlying functions where applicable) unreasonable, according to current modeling and peer-review practices? If so, please explain.

b. Are these methodologies scientifically justified for the purpose for which they are used? If not, what problems exist and how should they be addressed? Please explain what changes might be considered and provide references (if any).
c. For feature C5 (approach to defining diets), a test case is provided for modeling chronic chemical hazard in a multifood risk scenario. Are there other food safety issues or situations where this feature could be applied, such as modeling nutrients or nutrition-related issues? If so, please provide suggestion(s) and reference(s).

3. For features B2, C1, C3 and C4, please review the FDA-iRISK tool and test cases provided.
   a. Are these features adequate for the intended purpose? If not, please explain what changes might be considered and how they would improve the feature(s).
   b. For feature B2, are the import files provided adequate to demonstrate the functionality of the feature? If not, please explain what changes or additions might be considered.
   c. Considering the test cases provided, are they adequate to demonstrate the functionality of the new features? If not, please explain.

4. For features in group D, please comment on the FDA-iRISK user interface. Is any of the features (D1 through D5) not user friendly? Are any of these features or descriptions of the features that could be enhanced to facilitate ease of use?

5. Comment on the FDA-iRISK 5.1 Technical Document sections relevant to the new features, with a focus on those in Groups A, B and C. Is it sufficiently clear in the description of the modeling approach, mathematical functions (where applicable), and other aspects to document the validity of the underlying model structure of FDA-iRISK? If not, please identify which aspects are unclear, and what changes should be considered to improve clarity and transparency.

6. The Office of Management and Budget (OMB) memo M-19-15, Improving the Implementation of the Information Quality Act (https://www.whitehouse.gov/wp-content/uploads/2019/04/M-19-15.pdf), notes that information disseminated by each federal agency be fit for its intended purpose, and that each agency considers the appropriate level of quality for each of the products it disseminates based on the likely use of that information. Given the intended purpose of FDA-iRISK, please comment on the utility, integrity, and objectivity of the model in general and the specific new features specifically.

7. Do you have comments on how the FDA-iRISK tool might be applied more broadly to support risk prioritization? Do you have any additional comments? Please share them in your review.

Appendix I. FDA-iRISK 5.1 new features organized in groups

Group A includes new features useful for the Process Model: linkage to ComBase (A1 through A8), and linkage to the FDA-OC App (A9). Group B includes features useful for the Consumption Model. Groups C includes features useful for the Risk Scenario. Group D includes features for User Interface Experience.

Group	ID	Feature Name
A	A1	Import ComBase record growth and inactivation model fits
	A2	Import ComBase DMFit growth and inactivation model fits
	A3	Import ComBase Broth Model predicted growth
	A4	Import ComBase Perfringens Predictor predicted growth
	A5	Import ComBase thermal inactivation models
	A6	Import ComBase non-thermal survival models
	A7	Import ComBase *Salmonella* in egg models
	A8	Growth by Model process stages no longer require a temperature distribution when applying imported ComBase models
	A9	Import microbial sampling plan OC curve from FDA-OC App
B	B1	Correlation of consumption across life stages for chronic multifood consumption models
	B2	Import chronic multifood consumption models
	B3	Chronic multifood consumption models parameterized by consumers-only distribution and percentage of consumers in the distribution for per capita distribution
C	C1	Result tab on the Edit Risk Scenario page showing list of reports, summary of risk estimates, and options for visualization
	C2	Visualization of intermediate and final results for microbial and chronic chemical scenarios, including C2_a: Results visualization for single food, single hazard acute microbial scenarios results C2_b: Results visualization for single food, single hazard chronic chemical scenarios results C2_c: Results visualization for multifood food, single hazard scenarios results C2_d: Results visualization for multifood food, multi-hazard scenarios results C2_e: Concentration charts for the distribution of microbial concentrations in contaminated products across process stages for single food, microbial scenarios
	C3	Sensitivity analysis for chronic multifood, multi-hazard scenarios
	C4	Multifood models with pre-run process models for concentration
	C5	Expanded and more flexible approach to defining diets

Group	ID	Feature Name
D	D1	Copy hazard feature enhanced to allow copies between repositories
	D2	Copy food feature enhanced to allow copies between repositories
	D3	Copy process model feature enhanced to allow copies between repositories
	D4	Add references to notes (D4_a) and add images to notes (D4_b)
	D5	Exclude repeated scenario details in sensitivity analysis risk estimate reports

III. SUMMARY OF PEER REVIEWER COMMENTS AND FDA'S RESPONSE

Question 1: For Group A features, please review the FDA-iRISK tool, test cases, and the methodology (relevant sections) described in the FDA-iRISK 5.1 Technical Document provided.

Question 1a: For features A1 through A7, is the linkage to ComBase adequate to capture the outputs from ComBase (https://combase.errc.ars.usda.gov/) appropriately, and to upload the ComBase results accurately into the FDA-iRISK tool? If not, please explain what changes might be considered to improve the feature(s).

The reviewers appreciated the ComBase linkage feature and noted that export files of ComBase models were uploaded well. One reviewer noted that it would be "*helpful to get an explanation of the principles behind the navigation through the iRISK tool as it is done in the test cases. For example, the models are to be uploaded as features of the hazard, not of the model (the processing stages) itself. It is logical, but it requires a bit of thought before you realize that it is, and you might want to help the user here*."

A reviewer noted that "*Once a growth model is defined and included under the hazard tab, you do not see how the growth is actually modelled in the process model.*" A user must navigate back to the hazard tab to, for example, see the log increase associated with a selected time. The reviewer noted that in the test case for feature A3, in the Process Model, a user has a broth growth model and can enter a value for the time, but the user does not see how much growth is associated with the time in terms of log increase predicted; the user has to look this information up in the model itself under the hazard tab, to find out that, for example, 4-6 hours is associated with between 0.03 and 0.14 log increase.

The reviewer noted that it would be "*nice for a user if the input values of a ComBase model would be provided alongside the output*." For example, in the test case a *Salmonella* growth model at 20°C is obtained from ComBase, and the reviewer noted that it would be nice to see the relevant information (i.e., growth conditions) used in the ComBase model also included in the FDA-iRISK report. The reviewer also made a more general point that input values are provided in the Excel file (for growth or inactivation) from ComBase but do not seem to be taken up by FDA-iRISK. It would be nice if the growth or inactivation conditions are shown, either in the FDA-iRISK tool when working with it, or in the report.

One reviewer noted possible errors while uploading the ComBase results, for example, "*I filled in that the* Salmonella *in eggs model was an inactivation model and not a growth model. As a consequence, nothing showed up in the list of predictive models under the edit hazard tab*." An appropriate error message at this point (e.g., indicating that the type of model was incorrectly selected) would have been advantageous.

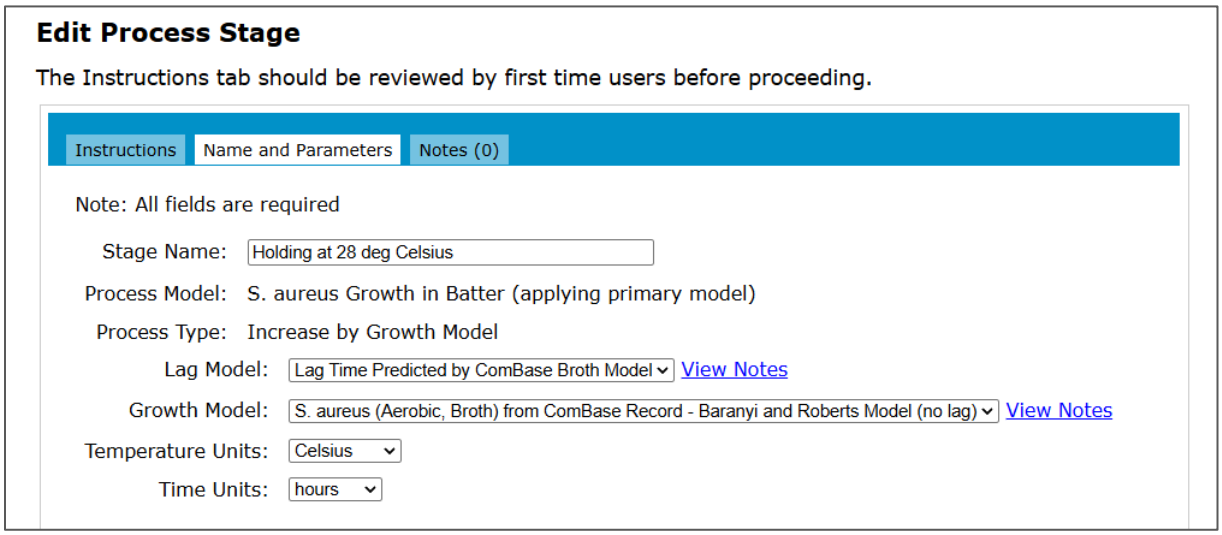
FDA Response:

We thank the reviewers for the comments and suggestions. We explain the rationale behind uploading ComBase models as features of the hazard in the FDA-iRISK 5.0 Technical Document (Ref. 1). A ComBase model, as is the case for any other predictive model for a microbial hazard, once uploaded or otherwise defined, may be used in multiple process models. We provide step-by-step guidance on how to add a ComBase model and any other predictive models for microbial hazards in the FDA-iRISK 5.0 User Guide (Ref. 2). To further help the user, we plan to explore additional ways to provide navigation assistance on the FDA-iRISK user interface, such as short instructional videos that highlight relevant contents in references 1 and 2.

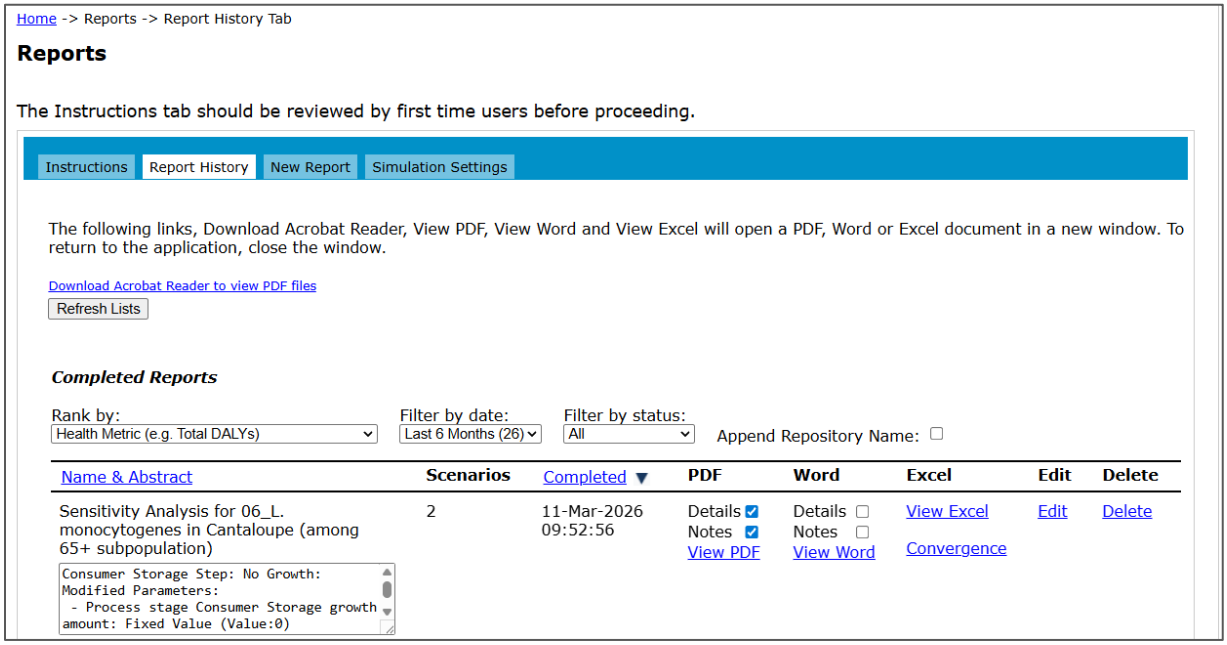
We agree with the reviewer that the user needed to navigate back to the Hazard tab to look up the log increase (e.g., concentration-time relationship) of the ComBase model. To provide the user quick access to the conditions of the ComBase model (e.g., growth model), we have added a new feature under the Process Stage tab where, when the user chooses "Edit" to define time for use to predict growth, they can now click a "View Notes" link (next to the Growth Model; see screenshot 1a-1) leading to the Notes page showing ComBase record details such as meta information, raw data points (if applicable), and the conditions for the ComBase model. Similarly, a "View Notes" next to a Lag Model is also provided.

The ComBase export file (Excel file) includes: a) input values for the predictive model that are usually taken up by FDA-iRISK as a concentration-time curve along with a table that shows the time-concentration data. Input values that are parameters of a predictive model, such as the D-value of a linear inactivation model, are taken up as parameters of the appropriate model. These are provided on the relevant page in the FDA-iRISK interface; b) growth or inactivation conditions are taken up by FDA-iRISK in the Notes page under the heading "ComBase Record Details", which may also include raw data points and conditions if available from the ComBase record or ComBase model. When the user generates a report in FDA-iRISK, the user can include the input values along with the notes associated with the ComBase model (e.g., for growth and for inactivation) that have been uploaded, by selecting (checking the box for) both Details and Notes when they select "View PDF" on the Reports –> Report History Tab (screenshot 1a-2).

Screenshot 1a-1.



Screenshot 1a-2.

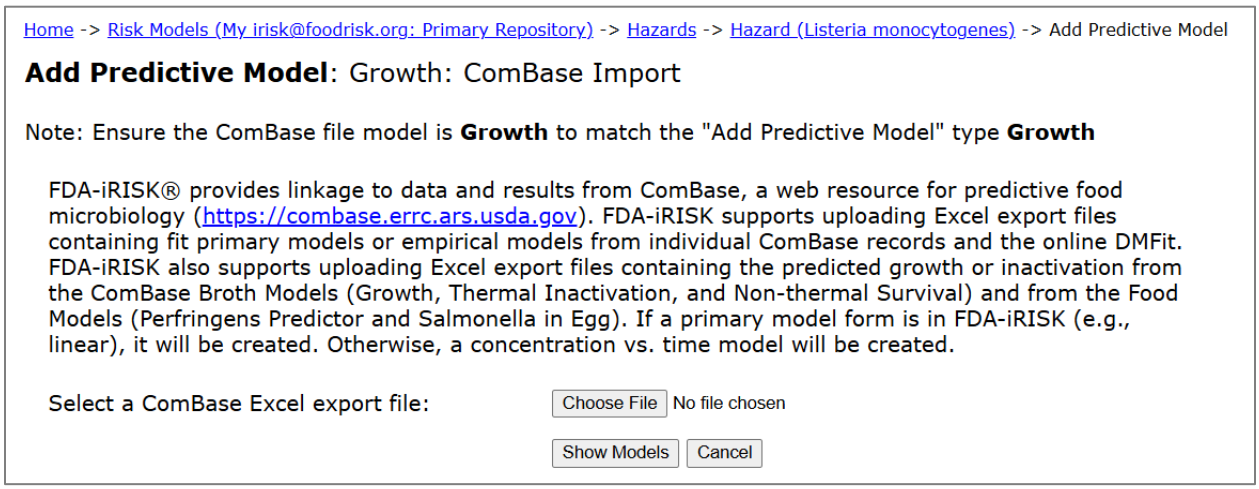


We agree with the reviewer that providing an error message or otherwise addressing the mis-match issue would be helpful. We were able to reproduce the mis-match situation, i.e., selected "Inactivation: ComBase Import" as model type, chose the ComBase output file A7, *Salmonella* in Egg (a file for growth model), and observed that the *Salmonella* in Egg model did not show up on the Edit Hazard -> Predictive Models Tab.

We have provided a reminder upfront for the user to ensure matching selected model type and ComBase file to be uploaded. For example, when the "Add Predictive Model" page indicates

"Add Predictive Model: Growth: ComBase Import", we have added on the page a reminder: "*Note: Ensure the ComBase file model is **Growth** to match the "Add Predictive Model" type **Growth***" (screenshot 1a-3). Similarly, when the user chooses to upload an inactivation model, the "Add Predictive Model" page show the following: *"Note: Ensure the ComBase file model is **Inactivation** to match the "Add Predictive Model" type **Inactivation**"*. We may consider other options in the future to address this issue such as providing feedback (error message).

Screenshot 1a-3.



Question 1b: For feature A8, is the rationale provided in the Technical Document appropriate for no longer requiring a temperature distribution when applying imported ComBase models? If not, please explain what changes might be considered.

A reviewer indicated that there was some confusion associated with the conditions for the ComBase models uploaded. Although all conditions may not be relevant to the specific process model being created, the reviewer noted that it would be useful to have the information included somewhere as "*an aid to understand what the process model is actually modelling*." More specifically, the reviewer commented that there is no mention of temperature and noted that "*I do not see how the 20°C is used that I have to fill in for temperature in the generic primary growth model: it seems not to have temperature as a parameter. So I do not understand the difference between the generic primary growth model and the ComBase model in relation to reference to the temperature" and that "it seems the temperature is asked for in the generic primary growth model, where it is not used. It is not asked for in the models coming from ComBase, where they may actually be given*."

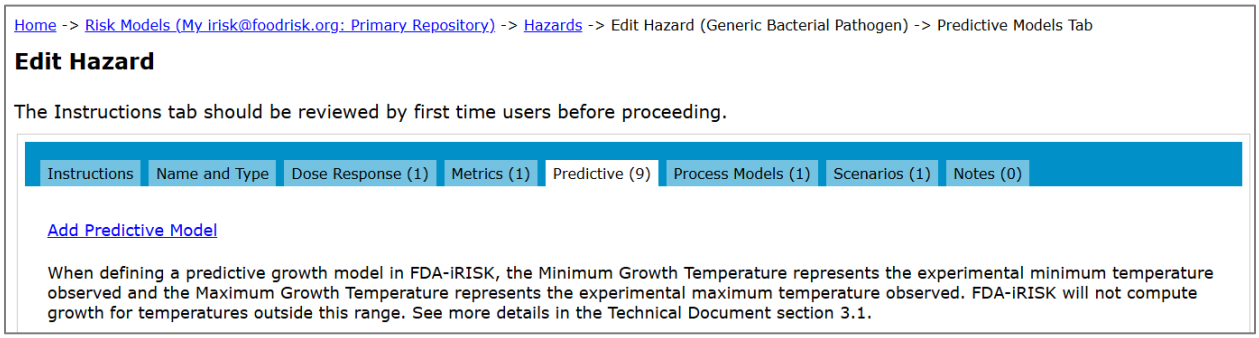
FDA Response:

We thank the reviewers for the comments. In response, we have added an explanation on two separate pages in the FDA-iRISK user interface on why Minimum Growth Temperature and Maximum Growth Temperature are required inputs when users add a predictive model (including a generic primary growth model and a model coming from a ComBase file). The

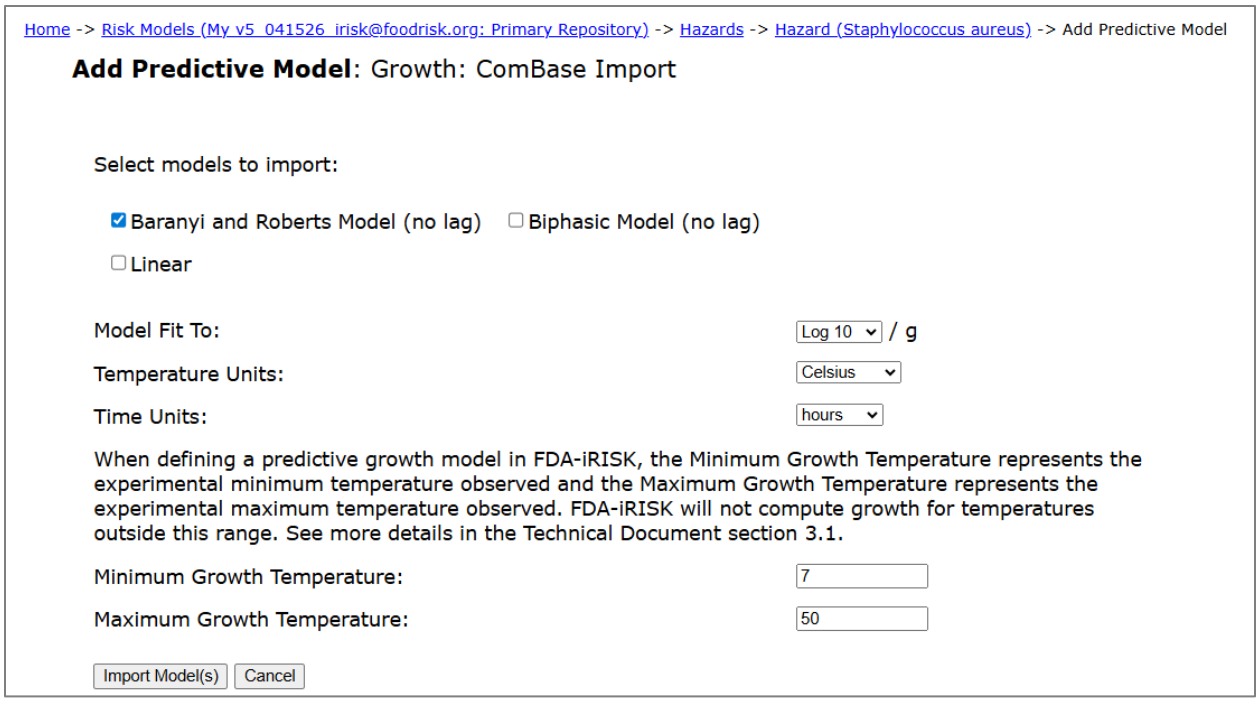
explanation also indicates that section 3.1 in the FDA-iRISK 5.0 Technical Document (Ref. 1) provides more details. For both a generic primary growth model and an imported ComBase growth model, FDA-iRISK uses the minimum and maximum temperatures and will not compute growth for temperatures outside this range, e.g., in sensitivity analysis, if the user enters a temperature outside of this range.

The screenshots (1b-1 and 1b-2) below are the pages that display the explanation. The user will see the explanation when they navigate from under the Edit hazard –> Predictive Models Tab to these pages to upload or create a predictive model.

Screenshot 1b-1.



Screenshot 1b-2.



Question 1c: For feature A9, is the linkage to the FDA-OC App adequate to capture the outputs from the FDA-OC App (https://foodsafetyrisk.org/OC/) appropriately, and to

upload the OC curve results accurately into the FDA-iRISK tool? If not, please explain what changes might be considered to improve the feature.

The reviewers verified that they were able to upload the OC curve results accurately into the FDA-iRISK tool. One reviewer noted that the application of the OC curves was not provided as part of the feature A9 instructions, and thus the reviewer did not test that.

FDA Response:

We thank the reviewer for the positive comments. Feature A9 is intended for uploading OC curve file. The application of the OC curves is described elsewhere in the FDA-iRISK 5.0 Technical Document (Ref. 1) that had been subject to a previous peer review.

Question 2: For features B1, B3, C2 and C5, please review the associated Analytica files and the methodology (relevant sections) described in the Technical Document. Evaluate whether the new features are adequate according to current modeling and peer-review practices.

Question 2a: Are any of the assumptions associated with the methodologies for these features (including the underlying functions where applicable) unreasonable, according to current modeling and peer-review practices? If so, please explain.

In general, the reviewers found that the methodologies for the B1, B3, C2, and C5 are reasonable and consistent with current modeling practices, and that these new features provide users with flexibility to modify underlying assumptions and data input and generate good visualizations. The reviewers did not find unreasonable assumptions in the methodologies.

For C2, one reviewer noted that it was difficult to find *"specific sections in the Technical Document referring to the issues in the test cases, comparing and showing risk scenarios."*

FDA Response:

We thank the reviewers for the positive comments. Regarding C2, we agree that multiple sections in the technical document describe the methodologies underlying the "Visualization of intermediate and final results for microbial and chronic chemical scenarios." Indeed, for this peer review we left the navigation of the technical document up to the reviewer. In the future, we can consider pointing out the relevant technical documentation sections in the instructions provided for each test case. For example:

- For test case "C2_a: Results visualization for single food, single hazard acute microbial scenarios results" and test case "C2_e: Concentration charts for the distribution of microbial concentrations in contaminated products across process stages for single food, microbial scenarios," the applicable sections in the FDA-iRISK 5.0 Technical Document

(Ref. 1) would include: sections 1.1, 1.2, and 1.3.1 "Probability of Illness: Acute Hazards," and section 2 "Estimation of the Extent of Contamination: Process Models," specifically section 2.3 "Process Types for Microbial Hazards."

- Section 2.1 "Description of Initial Contamination" would apply to test cases C2_a and C2_e.
- Section 2.3.1 "Increase by Growth – Microbial" and section 2.3.3 "Increase by Addition – Microbial" would apply to test case C2_a (a risk scenario on *Listeria monocytogenes* in cantaloupe).
- Section 2.3.6 "Decrease – Microbial" and section 2.3.10 "Partitioning – Microbial" would apply to test case C2_e (a risk scenario on *Salmonella* spp. in peanut butter).

Question 2b: Are these methodologies scientifically justified for the purpose for which they are used? If not, what problems exist and how should they be addressed? Please explain what changes might be considered and provide references (if any).

The reviewers generally commented that a user's ability to account for correlation of food consumption between life stages and between foods in FDA-iRISK was comprehensive. They pointed out three separate issues.

First, regarding feature B1, a reviewer noted that "*…the user's options and models to modify correlations are comprehensive and well described in the technical document and easy to follow in the test cases (B1.a. and B1.b). These options to facilitate sensitivity analysis are consistent with conventional modeling practices.*" However, the reviewer noted that the method of aggregation of chronic exposure from all foods that are being assessed under a Multifood Single Hazard scenario or Multifood Multihazard scenario was not explicitly described in the FDA-iRISK 5.1i Technical Document. Based on the description on a relevant page and a figure in the document, the reviewer assumed that the aggregation is a sum of exposure across all foods that are under consideration in a Multifood scenario. The reviewer noted that *"… not all foods would be consumed by an individual in a given day. Typically, in an intake assessment using nationwide food consumption surveys, the consumption of multiple foods is assessed at the individual level so that joint food consumption can be derived, since not all foods under consideration would be consumed in a given day. As such, if the model is adding across all foods, the estimates in more complex with Multifoods scenarios are likely overestimates. Users should be made aware of this so that proper interpretation can be made*."

Regarding feature B3, a reviewer was confused by the "distribution warping" feature and commented that the explanation in the technical documentation was insufficient. The reviewer was not aware of the term "warping" and commented that it was not technically intuitive to understand, and that the term was not clearly explained on several relevant pages in the FDA-iRISK 5.1i Technical Document.

Finally, in a separate comment regarding feature B3, one reviewer encountered an error that they were unable to reproduce: when evaluating the feature, under the "Edit Multifood Life Stage and Consumption" page, at some points the "Modified Consumption Distribution" did not show.

FDA Response:

We thank the reviewers for the comments and suggestions. Regarding the general comments on B1, we note that FDA-iRISK provides the capacity for the user to define correlation of food consumption between life stages for a food, and they may define such correlation (for each food) individually for some or all foods in a multifood risk scenario or an exposure scenario. However, feature B1 does not provide the capacity for users to define correlation between foods; users may explore that indirectly by using different diets.

To address the reviewer's comments on the method of aggregation of chronic exposure from all foods, we have added a new paragraph to section 4.3.1 in the FDA-iRISK 5.0 Technical Document (Ref. 1).

Regarding the comments on B3, we agree "warping" is an obscure term in food safety risk assessment. We have decided to use "Exponential Percentile Adjustment" to replace the term "warping" and added text to clarify that this function is to provide a convenient non-linear option for exploratory analysis in section 4.4.5 in the FDA-iRISK 5.0 Technical Document (Ref. 1).

We thank the review for sharing the observation that *"at some points the 'Modified Consumption Distribution' did not show, but I was not able to reproduce that error."* We tested several times on the "Edit Multifood Life Stage and Consumption" page and did not observe an error (the feature worked as expected).

Question 2c: For feature C5 (approach to defining diets), a test case is provided for modeling chronic chemical hazard in a multifood risk scenario. Are there other food safety issues or situations where this feature could be applied, such as modeling nutrients or nutrition-related issues? If so, please provide suggestion(s) and reference(s).

A reviewer commented that although this was not their main area of expertise, "*the approach to model shifts in the diets is understandable and seems right*." They suggested that in principle, "*you may be able to apply the methods for chronic chemical hazards also to nutritional hazards, and even to nutritional benefits, if only you have comparable 'dose response relations*"' for the analysis. The reviewer also indicated that nutritional analysis *"... is probably the challenge, as that is not the way of thinking in nutrition, where one for example has to deal with the effects of substitution*" because if consumers stop eating one thing, they may start eating something else that has health effects as well. The reviewer noted that substitutions will become pretty complex to take into account.

The reviewer noted that, "*The way diets are modelled now is as a combination of foods with one or more identical hazards. As long as there is a clear link between the hazard(s) (chemical(s)) in the food(s) and a health endpoint for which we have a dose response relation, this is a wonderful opportunity to assess the total combined exposure and risk."* The reviewer suggested that the approach in FDA-iRISK may not be valid in certain cases when interactions come into play, or when dose response depends on underlying (lifestyle) factors, sex and age, where the analysis may get more complicated. For this reason, the reviewer commented that they do not think *"...the iRISK approach would be the most efficient when doing risk-benefit assessments of foods involving diets*." Furthermore, the reviewer commented that what approach to take for risk-benefit assessments involving diets is still an unanswered question in the field. The reviewer provided a reference that further discusses how to meet challenges in the development of risk-benefit assessment of foods (a paper published in *Trends in Food Science and Nutrition* https://doi.org/10.1016/j.tifs.2018.04.004).

The reviewers encountered several issues when testing feature C5. Issue (1) is:

> "*When you are in the Edit Diet page, consumption models tab and click one of the edit links, you have to go to the diet at the link in blue under the table to see which food you clicked. I would have expected it in the text of the Diets tab. You cannot go back directly to the consumption models table where you were before, which is a bit confusing when navigating through the tool. A link would be helpful*."

Issue (2) is that the difference between "C5 No diet" and the "C5 Diet baseline" was unclear; the reviewer saw "*no difference between the two...*," but they were presented under different names that seemed to suggest there was a difference. The reviewer noted that, regarding the risk estimate of losses in Disability-Adjusted Life Year (DALY):

> "*14000 DALY estimated in the baseline for C5 Diet, are not found for C5 Diet in the report.... For the C5 scenario I see the 14000 DALY mentioned at the lower end of the page, in the table, but for No Diet I do not find the total DALY. I see the 14000 are mentioned on page 2 and 3, but I expected them on page 12 as well*."

A reviewer noted that the diet modification options (e.g., based on simply changing the percent consumers and/or shifting the consumption distribution) are useful for "what if" assessments, particularly in cases where there is a risk/benefit trade off (e.g., methylmercury vs omega-3 in fish). However, the reviewer noted that, while the model may work well for a single food single hazard scenario, it is not evidently clear how scenarios involving multiple foods (e.g., pesticides vs phytonutrients in fruits and vegetables) can be implemented. The potential for overestimation in aggregating across foods (see Question 2b comments) is more of an issue with nutrients, where the concern is under (not enough nutrients or shortfalls) and not over (exceedance).

Further, usual intake is used in nutrient assessment, so users should be made aware of the data needed when attempting nutrient assessment.

Another reviewer commented that feature B3 (modify diets) and feature C5 are related, and that the test case could have been more efficient with collapsing these two test sections into one.

Some reviewers noted that for the diet feature, a user is only able to add one food at a time. The option to select multiple foods in the drop-down menu would be useful. They noted that the shift for percent consumers in the diet feature was logical, but the basis for the linear and warping options was unclear. Finally, the process to create a report from a diet scenario involves multiple steps which the reviewer noted may be confusing for users if they do not have the step-by-step instructions as provided in the test case.

FDA Response:

We thank the reviewer for the comments regarding the complexity and challenges involved in applying FDA-iRISK methods for modeling risks from chronic chemical hazards to modeling multiple facets related to nutrients, nutritional hazards, and nutritional benefits. We agree that currently comparable "dose response relationships" for such analysis may not be available. We thank the reviewer for providing the reference and suggestions. We will continue to learn from the scientific literature on key challenges and potential solutions in risk-benefit assessment of foods related to methodologies, data needs, and health metrics. We plan to identify opportunities to potentially expand the capacity of FDA-iRISK by tapping into advancements in the field of risk-benefit assessment to address these challenges.

Regarding the issues the reviewers encountered when testing feature C5 (Issue 1), we acknowledge that there is a lot of content, and the user needs to navigate a few tabs to make changes in the diet. The comment suggests that more training is necessary to make it easier to use feature C5. We will also evaluate feasibility and consider adding a link to allow the user to go back directly to the consumption models table from the Edit Multifood Life Stage and Consumption (Complete Lifespan)-> Diets Tab.

We agree with the reviewer that the navigation of the diet feature for editing can be a bit confusing. For example, let's assume we want to make a change using the method "Linear Amount Adjustment" for Food 1 in the Shift "F1 Lower, F2 Higher." Currently, such a change involves what the reviewer described, including the following:

> If the change leads to, e.g., changing from "F1 Lower, F2 Higher" to "F1 None, F2 Higher," the user needs to navigate back the Diet -> Name and Parameters page to edit the name of the shift to "F1 None, F2 Higher." Alternatively, the user can plan ahead, e.g., edit the name of the shift first, and then proceed to the Edit Multifood Life Stage and Consumption (Complete Lifespan)-> Diets Tab to change F1 consumption.

For the comment on which food the user clicked, as the reviewer noted, this information is shown on the Diet tab, in Quick Links at the bottom of the page.

We thank the reviewer for the comment related to Issue 2. We acknowledge that providing two scenarios and two Analytica model files might suggest a difference; our intention was to show that there is a difference between the C5 diet shifts and C5 Diet baseline, and that there is no difference between the "C5 No diet" and the "C5 Diet" baseline. We provided the "C5 No diet" Analytica model file because it is simpler to review than the nodes and functions specific to the baseline in the "C5 Diet" Analytica (which has a lot more nodes and functions associated with the diet shifts). To avoid this confusion, we could have provided a note upfront in the C5 test case document.

We did provide a note in Test 2 Step 11 of the test case document that indicates

> *"Review the report starting on the bottom of page 4 and note how the diets have altered the results for risk in each case. Compare the baseline for the C5 Scenario with the No Diet version. The values should be the same".*

For example, 14000 DALYs is risk estimate for the "C5 No Diet" scenario and for the "C5 Diet" baseline scenario.

We thank the reviewer for the positive comment regarding the utility of the diet modification options for "what-if" assessments. To make it clearer that diet modification options also apply to scenarios involving multiple foods and chronic hazard(s), we provided instructions in the FDA-iRISK 5.0 User Guide (Ref. 2) in Chapter 4 Diets: i.e., "Including a Diet in a Multifood Risk or Exposure-Only Scenario" and "Refer to the section Adding a Risk Scenario, Computed (Multifood) or Adding a Risk Scenario, Computed (Multifood, Exposure Only) in Chapter 7 for details on applying a diet to a multifood scenario."

We also provided an example (a sample scenario) in FDA-iRISK 5.0, which is shared with registered users through the "irisk@foodrisk.org: Primary Repository". The sample scenario "v5_10_Manganese in Fruit & Vegetables (with dietary shift)" includes a "Fruit and Vegetable NHANES Diet" to illustrate how a diet shift, e.g., a 20% increase in the amount consumed for 11 fruit and vegetables, is predicted to change exposure to the nutrient (manganese) and risk associated with potential Mn deficiency (shortfalls) or Mn toxicity (exceedance).

We agree with the reviewer that it may be helpful to provide an example multifood scenario on how the diet features may be applied to chronic exposure to multiple nutrients or chemical hazards. This is a potential enhancement for the future, and we will take into consideration the reviewer's comments, including the need for additional data, for addressing issues related to potential overestimation in aggregating across foods and for addressing other comments on methodologies as described elsewhere in our response to Question 2c comments.

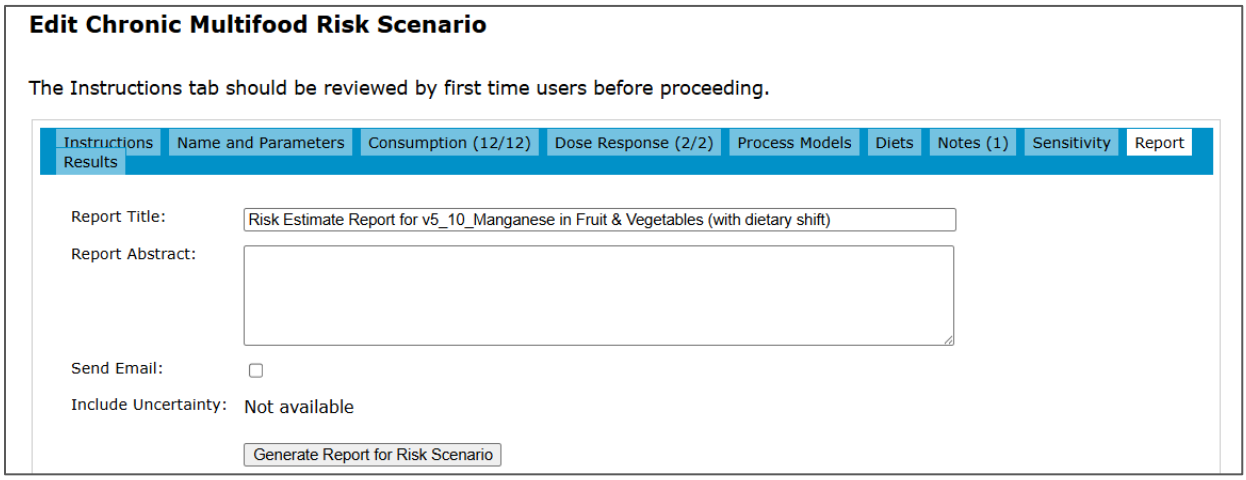
We have updated a diet-related feature in the FDA-iRISK user interface to enable selecting multiple foods in the drop-down menu; this update is now available in FDA-iRISK 5.0.

We thank the reviewer for the positive comment on shifting the percent consumers. For scaling the amount consumed, we have revised the two options to: 1) Linear Amount Adjustment, and 2)

Exponential Percentile Adjustment (this replaces the term "Warping"). For option 1, the basis is that consumers may choose to change the amount consumed for certain foods, e.g., increase consumption of fresh vegetables. For option 2, we clarified that, although a published reference is not yet available for food consumption use case based on an exponential percentile adjustment factor, this is an option to quickly shift a consumption distribution to various shapes (e.g., symmetrical, light-tailed, heavy-tailed) for exploratory analysis.

To create a report with the new diet feature, the FDA-iRISK 5.0 user interface provides a "Report" option under the tab "Edit Chronic Multifood Risk Scenario" (screenshot 2c-1). We acknowledge that the multiple steps involved in creating a diet could be confusing to navigate; the User Guide (Ref. 2) provides step-by-step instructions, and training may be necessary for users to become familiar with how to create a diet and run a report.

Screenshot 2c-1.



Question 3: For features B2, C1, C3 and C4, please review the FDA-iRISK tool and test cases provided.

Question 3a: Are these features adequate for the intended purpose? If not, please explain what changes might be considered and how they would improve the feature(s).

In general, the reviewers found that features B2, C1, C3, and C4 worked as intended and were well implemented. The new feature of pre-run processed models was emphasized as a good improvement for efficiency.

A reviewer provided specific feedback related to charts for concentration and prevalence over process stages, where there were multiple overlapping lines for the different scenarios (figures provided), and some scenarios labeled the second process stage as S1 when it should have been labeled as S2. More specifically, the reviewer stated, "*I struggle with the line graphs for 'Concentration and Prevalence over Process Stages.' Lines are overlapping. This is a problem if*

you see two lines that overlap others. You cannot see which one overlaps which. This overlapping line issue is found in all test cases with such lines," and "*The R3 scenario skips the first process stage and next takes the second one as "S1". So in the graphic it shows a result at S1, which actually, in comparison with the others, should fit with S2. This is confusing*." The reviewer noted the same issues in test cases C2_c and C_2e.

A reviewer commented that the C3 test case (for sensitivity analysis for chronic multifood multihazard scenario) was easy to follow, but generating a report for a multifood multihazard scenario was slow.

Regarding feature C3, another reviewer noted that the feature seemed to function as intended. However, the reviewer noted that the FDA-iRISK report generated from the test case (i.e., a chronic multifood, multi-hazard scenario) is extensive and can be quite difficult to comprehend. They suggested that, in future FDA-iRISK development, it may be possible to use AI Language Model to interrogate the report, summarize information of interest, and highlight key information for the reader.

Regarding feature C4, one reviewer commented that both test case 1 and test case 2 worked well and there were no issues using pre-run processed models for concentration (multifood single hazard). The reviewer was able to run process models associated with a multifood scenario and access stored results. The reviewer also confirmed that process models are only run when their parameters are modified for sensitivity analysis when a scenario is set to use existing process model results. The reviewer commented that this new feature of pre-run processed model is a good improvement in efficiency.

Another reviewer provided comments pertaining to the clarity of the Process Model Report versus Risk Estimates Report. In general, the reviewer noted that it is useful to re-use existing models, and this seems to work well. However, it was challenging to get the important details when reading the reports. More specifically, the reviewer noted that

- *"… the Process Models report gives different information from the Risk Estimate Report. In the second run (test 1) I added two scenarios, and I do not see the results of those in the Risk Estimate Report. What if I want another Process Model report for all of them, or the two added ones? It seems you get a Process Model report if you Run a Selection of process models and a Risk estimate report if you run All. This is not logical to me...."*.
- The reviewer further noted that *"I get different process model outputs even though the model inputs were the same for the Process Models report and the Risk Estimate Report. These are the same. I get different reports, containing different additional information. So I was mainly struggling with the fact that there are two different types of reports, where it was not clear to me when I get which one, or why there should be two types of reports in the first place."*
- The reviewer also noted that after re-doing the test, *"… I get the Process Model report via the 'Process Models' tab after running the models under the risk scenarios, and the*

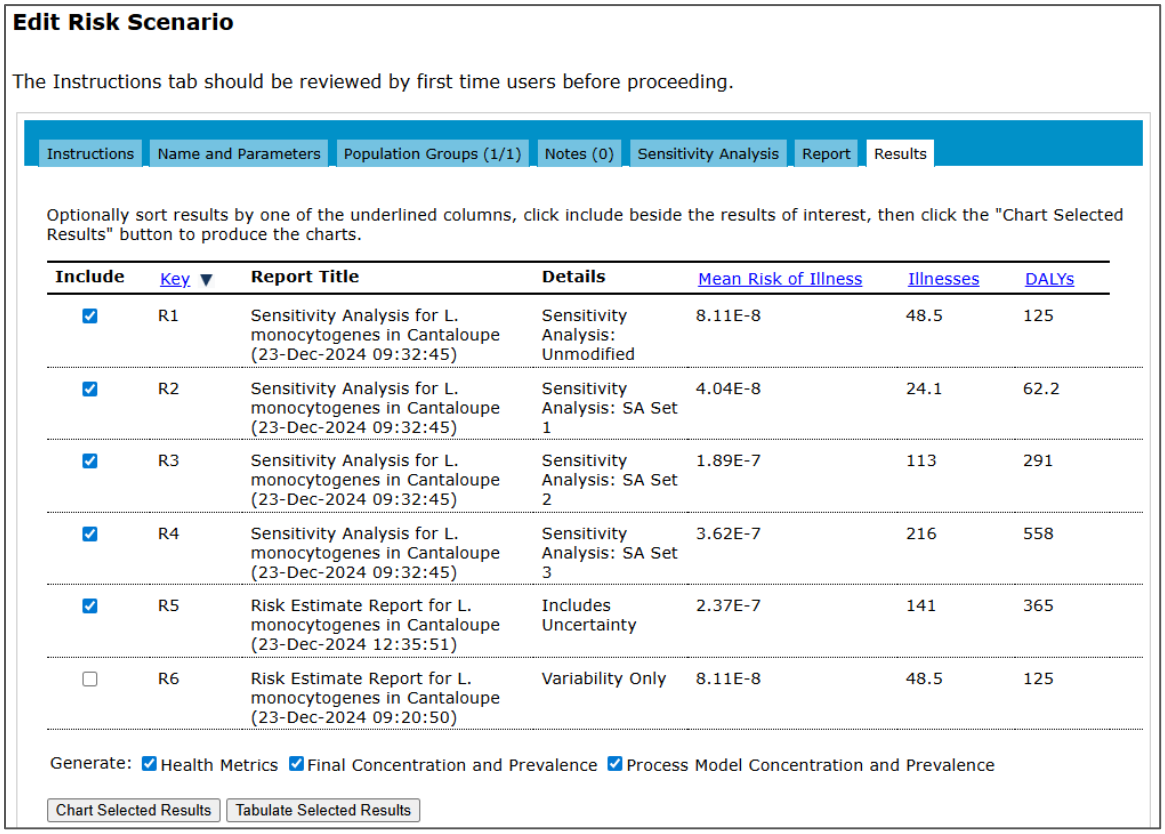
Risk Estimate report via the 'Report' tab after generating a report. If that is the idea, then it works."

FDA Response:

We thank the reviewers for the positive comments on features B2, C1, C3 and C4, and for confirming that the test cases for B2, C1, C3 and C4 worked as expected.

For the comments regarding C1, to address the issue of overlapping lines, we have added a new option "Tabulate Selected Results" (screenshot 3a-1), which complements the option "Chart Selected Results." Users can now obtain tabulated values corresponding to the charts (see example in screenshot 3a-2). We have updated the relevant feature such that the R3 scenario visualization now shows the step as S2 (not S1) in all the relevant charts (screenshot 3a-3). Similarly, for C2_e, users can help differentiate overlapping lines that show the same results (e.g., screenshot 3a-4) by choosing to tabulate the selected results (e.g., screenshot 3a-5).

Screenshot 3a-1.



Screenshot 3a-2.

Final Concentration and Prevalence

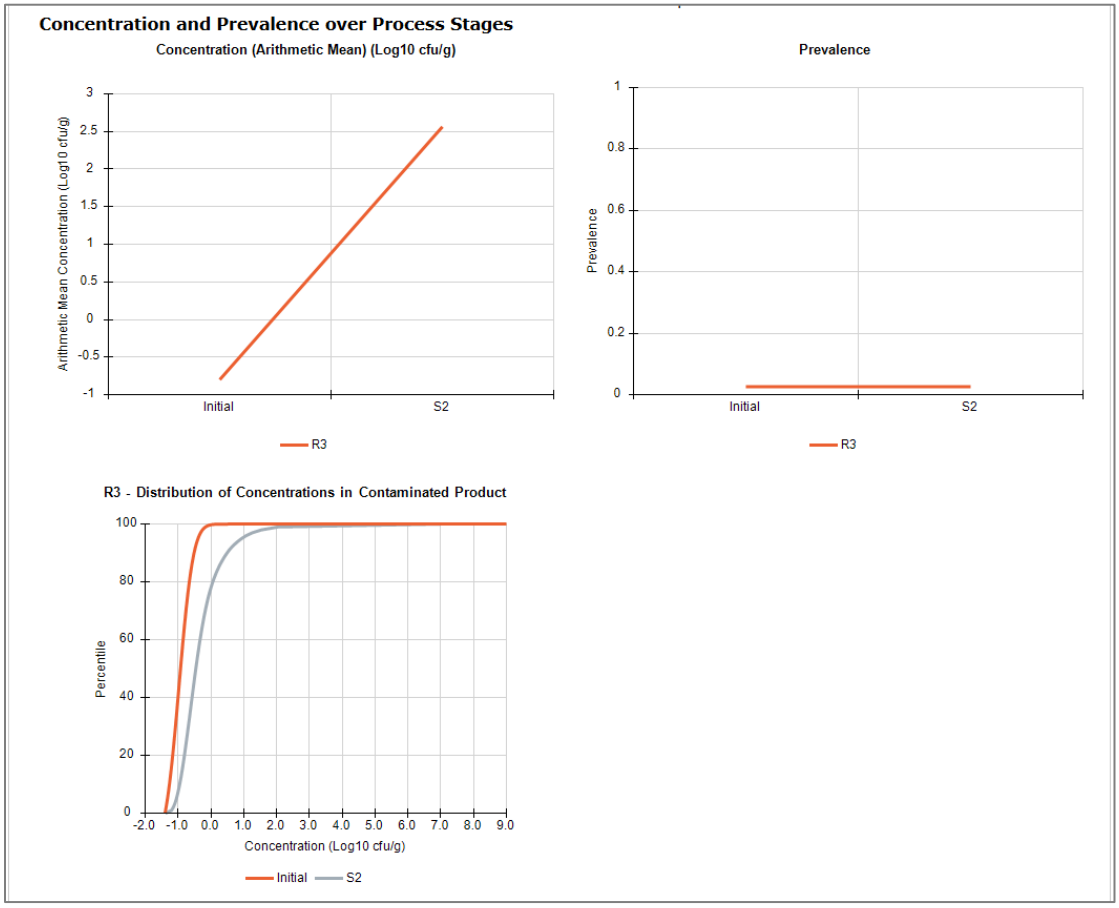
Key	Arithmetic Mean Concentration (Log10 cfu/g)	Prevalence
R1	2.53	0.0135
R2	2.53	0.00700
R3	2.56	0.0260
R4	2.51	0.0624
R5	2.53	0.0404

Distribution of Final Concentrations in Contaminated Product

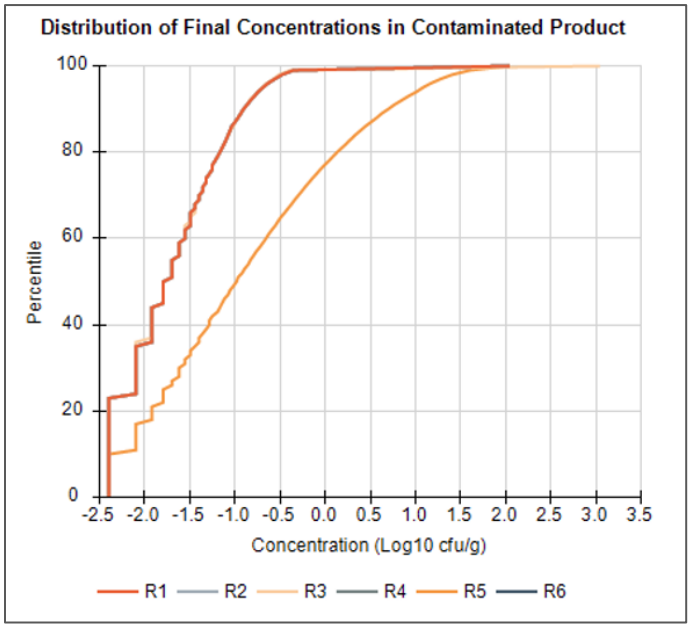
	Concentration (Log10 cfu/g)				
Percentile	R1	R2	R3	R4	R5
0	-1.38	-1.38	-1.39	-1.38	U*
1	-1.2	-1.19	-1.2	-1.14	U*
2	-1.14	-1.14	-1.15	-1.09	U*
3	-1.11	-1.1	-1.11	-1.05	U*
4	-1.08	-1.07	-1.08	-1.01	U*
5	-1.05	-1.05	-1.05	-0.988	U*
6	-1.03	-1.02	-1.03	-0.964	U*
7	-1.01	-1	-1.01	-0.944	U*

Note: * Concentration estimates with uncertainty not shown. See risk estimates with uncertainty range in other table(s).

Screenshot 3a-3.



Screenshot 3a-4.



Screenshot 3a-5.

Health Metrics

Key	Total DALYs	Total Illnesses	Mean Risk of Illness per Eating Occasion
R1	55400	2.92E+6	0.000172
R2	84000	4.42E+6	0.000260
R3	66000	3.47E+6	0.000204
R4	67000	3.52E+6	0.000207
R5	62.4	3280	1.93E-7
R6	66900	3.52E+6	0.000207

Final Concentration and Prevalence

Key	Arithmetic Mean Concentration (Log10 cfu/g)	Prevalence
R1	0.338	0.0585
R2	0.338	0.0585
R3	1.23	0.0585
R4	0.338	0.0585
R5	0.352	4.19E-6
R6	0.338	0.0585

Distribution of Final Concentrations in Contaminated Product

	Concentration (Log10 cfu/g)					
Percentile	R1	R2	R3	R4	R5	R6
0	-2.4	-2.4	-2.4	-2.4	-2.4	-2.4
1	-2.4	-2.4	-2.4	-2.4	-2.4	-2.4
2	-2.4	-2.4	-2.4	-2.4	-2.4	-2.4
3	-2.4	-2.4	-2.4	-2.4	-2.4	-2.4
4	-2.4	-2.4	-2.4	-2.4	-2.4	-2.4
5	-2.4	-2.4	-2.4	-2.4	-2.4	-2.4
6	-2.4	-2.4	-2.4	-2.4	-2.4	-2.4
7	-2.4	-2.4	-2.4	-2.4	-2.4	-2.4

We acknowledge that for a chronic multifood multihazard scenario, it may take some time to run the report. This is because it takes some time to cover multiple foods and multiple hazards in Monte Carlo simulation and to evaluate model convergence. To help set expectations, we plan to provide such context for users in future training.

We thank the peer reviewer for the feedback about the extensive test case report for feature C3. We agree that a very long report was provided for the C3 report. The report “Sensitivity Analysis

for Pesticides and Fruit and Veg" was 509 pages and generated using the option "Include All Scenario Details in Report" that included repeated details and data for each of the many scenarios added in the sensitivity analysis of the multifood multihazard risk scenario. FDA-iRISK now provides an option to "Include Only Unmodified Baseline Scenario Details in Report" to simplify the report, by excluding repeated scenario details of sensitivity analysis in the risk estimate report.

We thank the peer reviewer for the suggestion on the potential use of Language Model to interrogate the report, which we plan to explore for future FDA-iRISK enhancement. Moreover, we recognize that the emergence of Large Language Models (LLMs) has transformed how users research various risk assessment topics online and anticipate that users of FDA-iRISK will increasingly leverage LLMs to support their work. We plan to explore the appropriate utilization of artificial intelligence and machine learning such as LLMs to augment and support FDA-iRISK application to expedite quantitative, probabilistic risk assessments.

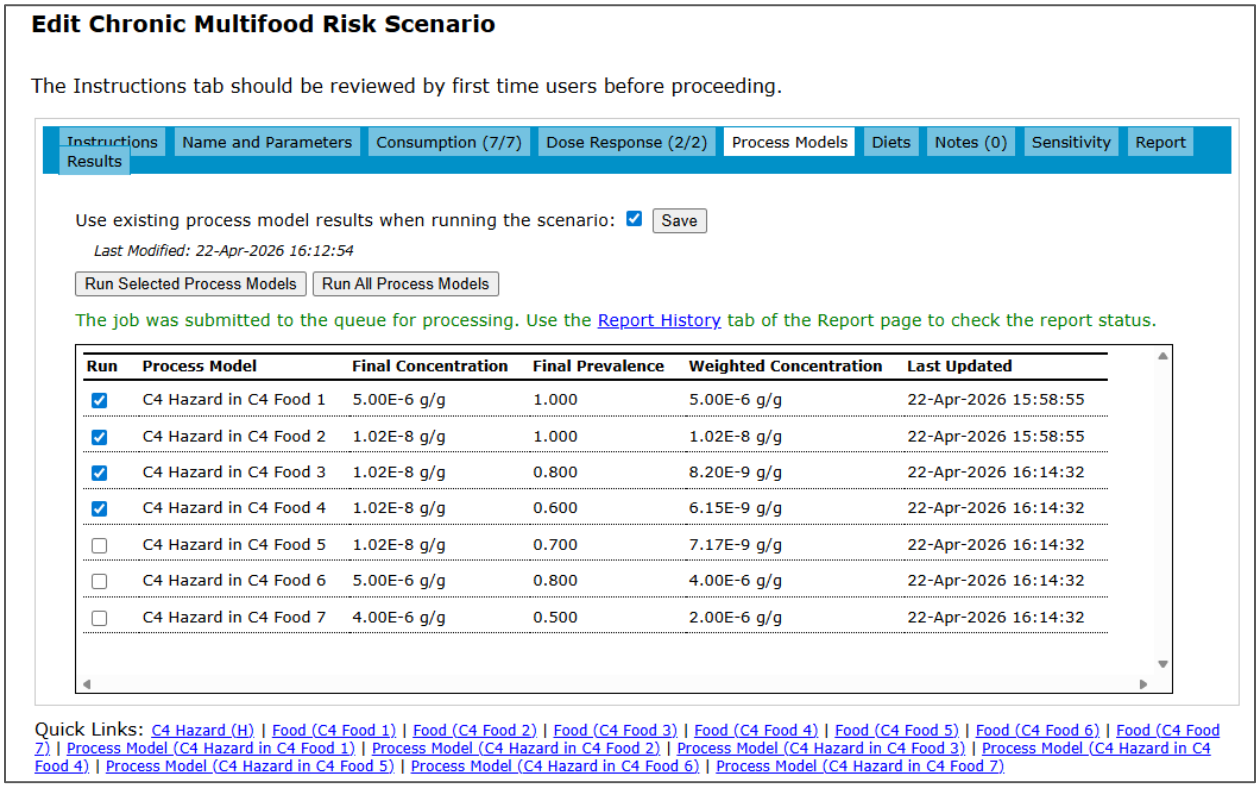
Regarding the observation that "the Process Models Report gives different information from the Risk Estimate Report," by design, when previously run process models are included in a risk estimate report, only the summary results from those process models are provided. On the other hand, for process models not previously run, complete results for these process models are provided in the Risk Estimate Report. The rationale is that complete results for the previously run models are available when they were run previously, which users can utilize.

After a Risk Estimate Report is submitted and completed (i.e., the first run) for Scenario C4 that includes seven process models, results from all the process models are completed and available for future use (screenshot 3a-6). If the user submitted a second run for a Risk Estimate Report, and checked and saved the option "Use existing process model results," the expected output is as the reviewer observed (i.e., we do not see the complete results for the seven process models in the second risk estimate report (instead, only summary results are provided) because all the process model had been evaluated in the first run and the existing process model results were used in the second run).

If users want a report for four (instead of two) process models, they can select the four process models of interest (e.g., as selected in screenshot 3a-6), FDA-iRISK will generate a process models report for the four selected (e.g., screenshot 3a-7), or for all seven process models if the users so choose. As the reviewer observed, users get a Process Model Report if they run a selection of the process models. Moreover, if they run a Risk Estimate Report, because the C4 scenario includes all seven process models, the report will include information about the seven process models. For example, from the first run the Risk Estimate Report includes summary results for the process models "Use existing process model results" and complete results for the process models not previously run. From the second run, the Risk Estimate Report includes summary results for all seven process models because all had been previously run. The rationale for not providing complete process model results in the run 2 Risk Estimate Report is that the complete results for the previously run models are available elsewhere.

The reviewer's comments suggest that it is complex for new users to navigate the features related to multifood models with pre-run process models for concentration, especially for users who do not usually work with this type of model. This will help inform future training efforts.

Screenshot 3a-6.



Edit Chronic Multifood Risk Scenario

The Instructions tab should be reviewed by first time users before proceeding.

Instructions | Name and Parameters | Consumption (7/7) | Dose Response (2/2) | Process Models | Diets | Notes (0) | Sensitivity | Report | Results

Use existing process model results when running the scenario: ☑ Save

Last Modified: 22-Apr-2026 16:12:54

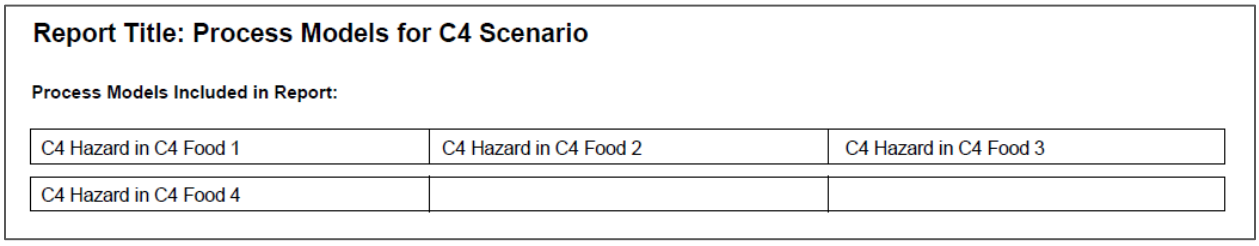
Run Selected Process Models | Run All Process Models

The job was submitted to the queue for processing. Use the Report History tab of the Report page to check the report status.

Run	Process Model	Final Concentration	Final Prevalence	Weighted Concentration	Last Updated
☑	C4 Hazard in C4 Food 1	5.00E-6 g/g	1.000	5.00E-6 g/g	22-Apr-2026 15:58:55
☑	C4 Hazard in C4 Food 2	1.02E-8 g/g	1.000	1.02E-8 g/g	22-Apr-2026 15:58:55
☑	C4 Hazard in C4 Food 3	1.02E-8 g/g	0.800	8.20E-9 g/g	22-Apr-2026 16:14:32
☑	C4 Hazard in C4 Food 4	1.02E-8 g/g	0.600	6.15E-9 g/g	22-Apr-2026 16:14:32
☐	C4 Hazard in C4 Food 5	1.02E-8 g/g	0.700	7.17E-9 g/g	22-Apr-2026 16:14:32
☐	C4 Hazard in C4 Food 6	5.00E-6 g/g	0.800	4.00E-6 g/g	22-Apr-2026 16:14:32
☐	C4 Hazard in C4 Food 7	4.00E-6 g/g	0.500	2.00E-6 g/g	22-Apr-2026 16:14:32

Quick Links: C4 Hazard (H) | Food (C4 Food 1) | Food (C4 Food 2) | Food (C4 Food 3) | Food (C4 Food 4) | Food (C4 Food 5) | Food (C4 Food 6) | Food (C4 Food 7) | Process Model (C4 Hazard in C4 Food 1) | Process Model (C4 Hazard in C4 Food 2) | Process Model (C4 Hazard in C4 Food 3) | Process Model (C4 Hazard in C4 Food 4) | Process Model (C4 Hazard in C4 Food 5) | Process Model (C4 Hazard in C4 Food 6) | Process Model (C4 Hazard in C4 Food 7)

Screenshot 3a-7. Excerpt of a "Process Models Report" that includes four process models



Report Title: Process Models for C4 Scenario

Process Models Included in Report:

C4 Hazard in C4 Food 1	C4 Hazard in C4 Food 2	C4 Hazard in C4 Food 3
C4 Hazard in C4 Food 4		

Question 3b: For feature B2, are the import files provided adequate to demonstrate the functionality of the feature? If not, please explain what changes or additions might be considered.

The reviewers indicated that the functionality of feature B2 was demonstrated well, in that the test cases provided were easy to follow and that the test cases show clear error messages when there are errors in the Excel files provided to evaluate importing chronic multifold consumption

models. One reviewer, however, noted the need for clear instructions on how to prepare new import files, as they were testing pre-made import files for the exercise.

FDA Response:

We thank the reviewers for the positive comments, confirming that feature B2 functioned as designed to properly import chronic multifood consumption models. Regarding the comment on how to prepare a new file, we have added instructions in Chapter 3 under "Importing a Consumption Model" in the User Guide (Ref. 2).

Question 3c: Considering the test cases provided, are they adequate to demonstrate the functionality of the new features? If not, please explain.

The reviewers commented that, in general, they found the test cases were adequate to demonstrate the functionality of the new features, albeit with the aforementioned points of confusion shared in response to Questions 3a and 3b.

FDA Response:

We thank the reviewers for the positive comments, confirming that the test cases for features B2, C1, C3, and C4 were adequate to demonstrate the functionality of these new features. See our responses to the comments in Questions 3a and 3b on these new features.

Question 4: For features in group D, please comment on the FDA-iRISK user interface. Is any of the features (D1 through D5) not user friendly? Are any of these features or descriptions of the features that could be enhanced to facilitate ease of use?

The reviewers found that most of the test cases were easy to follow. They indicated that the copying of a hazard, food, and process model into current and different repositories is user-friendly, as is the feature to exclude repeated details of model elements (i.e., for process model and other elements) in sensitivity analysis risk estimate reports. They indicated that the features were user friendly for those familiar with the underlying question and approach.

One reviewer had several questions about the interface for feature D3 – the inclusion of the food/hazard data when the process model was copied appeared inconsistent. More specifically, when a process model is copied to a new repository:

> "*…you have to click 'show food and hazard', but not when you copy to the same repository. The function of this button is not clear to me. When I do not click it for a new repository, there is nothing copied, whereas, when I click it for the same repository, it has no effect*".

Additionally, when copying a process model, there is the option to copy "existing food" or "existing hazard", and it was unclear the reasoning behind and the execution of this feature. More specifically:

> "*Step # 7 indicated there should only be one version of the hazard and food in the repository and they should show both process models under their "Process Model" tab. If I understand it correctly and did it correctly, this is not true as I see two versions. I get the impression that this feature deals with the issue that there can be different definitions of the same hazard (or food) in the different repositories*?"

A reviewer noted a lack of clarity regarding importing a shared repository throughout the exercises. Specifically, the process to import a shared repository was not intuitive. The reviewer recommended that the "view" and "import" steps be combined. One reviewer was also unable successfully "upload image" in relation to the ComBase model import.

FDA Response:

We thank the reviewers for the comments and suggestions.

Regarding the observations for feature D3 test 2, it is by design that when the user chooses a new repository to import the process model, a required step is to click "show food and hazard," which is required to "connect" to the new repository. In comparison, when the user chooses to copy to the same repository, the food and hazard from the same repository is already "connected." If the user does not click "show food and hazard" for a new repository, there is nothing copied because the user has not taken the step to "connect" to the new repository. As the reviewer observed, when the user clicks "show food and hazard" for the same repository, it has no effect because the food and hazard from the same repository (the currently chosen repository) is already "shown."

Regarding the reviewer's comments on feature D3 test 3, we agree that further explanation is necessary.

- First, the "use existing hazard" and "use existing food" options are depending on the completion of D3 test 2 in which the user had copied the process model to a new repository and had chosen the options to create a new hazard (i.e., *L. monocytogenes*) and a new food (i.e., Cantaloupe) and had clicked the "Copy" button. Completing D3 test 2 resulted in a process model "*L. monocytogenes* in Cantaloupe copy" in the new repository.
- Then, in D3 test 3, in the option "use existing hazard" the user selected the previously copied hazard (i.e., *L. monocytogenes*) and in the option "use existing food" selected the previously copied food (i.e., Cantaloupe).
- After steps a & b, the user clicked the "Copy" button that resulted in another process model "*L. monocytogenes* in Cantaloupe copy 2."

After completion of D3 test 3, the new repository will show the two process models on the "Process Models" page, i.e., the "*L. monocytogenes* in Cantaloupe copy" and the "*L. monocytogenes* in Cantaloupe copy 2" process models. These two process models share the same

hazard (i.e., *L. monocytogenes*) and the same food (i.e., Cantaloupe). This is what is meant by the instructions in D3 test 3 *"… there should only be one version of the hazard and food in the repository and they should show both process models on their 'Process Model' tabs."*

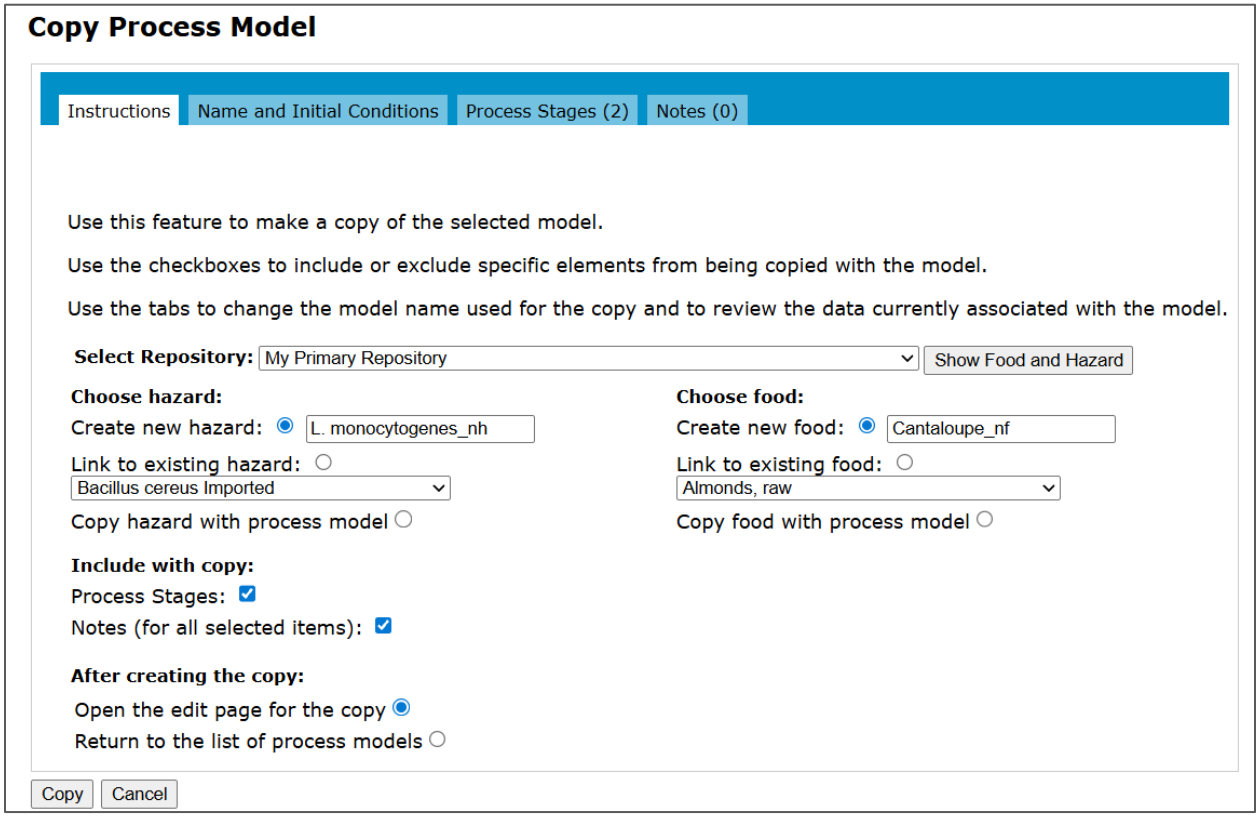
The reviewer is correct in their observation of two versions: this happened when the "new repository" already had a hazard (e.g., "*Listeria monocytogenes*_nr") and a food (e.g., "Cantaloupe_nr") defined before test 2 and test 3 were performed. The reviewer is correct that feature D3 deals with the issue that there can be different definitions of the same hazard (or food) in the same repository (e.g., the "new repository") or in different repositories.

FDA-iRISK provides three options (screenshot 4-1) to choose the hazard and the food when users copy a process model:

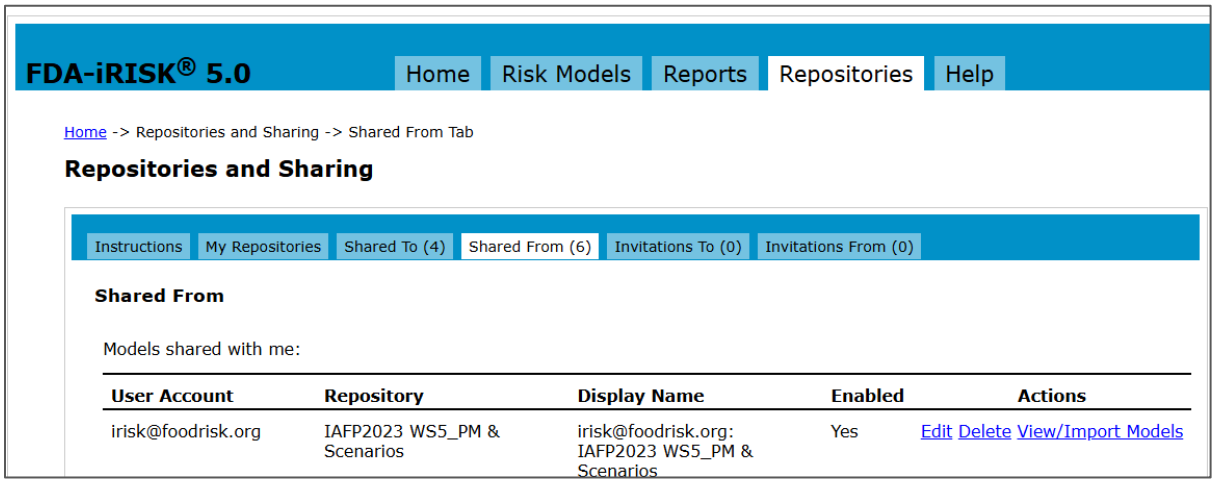
1) create a new hazard (e.g., named "*L. monocytogenes*_nh") and a new food (e.g., named "Cantaloupe_nf") as in D3 test 2. Note that in this option, no dose-response models have been defined for the hazard, and no consumption models have been defined for the food;
2) link to an existing hazard (i.e., "*L. monocytogenes*_nh") and link to an existing food (i.e., "Cantaloupe_nf") as in D3 test 3. Note that users can choose any of the existing hazard (e.g., the hazard "*Listeria monocytogenes*_nr" instead of the hazard "*L. monocytogenes*") and any of the food (e.g., the food "Cantaloupe_nr" instead of the food "Cantaloupe"); and
3) copy hazard with process model and copy food with the process model (e.g., resulting a new process model named "*L. monocytogenes* in Cantaloupe copy 3"). For example, assuming the process model to be copied is associated with the hazard "*L. monocytogenes*" and the food "Cantaloupe" in the repository "Peer Review Group D", and furthermore, there is a dose-response model defined for the hazard "*L. monocytogenes*" (named "Lm dose response for Adults 65+") and a consumption model defined for the food "Cantaloupe" (named "Cantaloupe Consumption 65+"). After the copy is completed, in the new repository, users will see the new process model named "*L. monocytogenes* in Cantaloupe copy 3", as well as the model "Lm dose response for Adults 65+" under the tab "Edit Hazard (*L. monocytogenes*)", the model "Cantaloupe Consumption 65+" under the tab "Edit Food (Cantaloupe)".

We have updated the FDA-iRISK user interface and changed "View Models" to "View/Import Models" under the tab "Shared From" (screenshot 4-2). More generally, the FDA-iRISK 5.0 User Guide (Ref. 2) provides information on how to import a shared repository, i.e., Chapter 10 Repository includes a section "Importing a Repository" that describes six steps for how users have the option to import shared repositories on the Risk Models page. Regarding the test case for uploading an image file, in FDA-iRISK 5.0, we did another test by uploading a reference and image file for the Process Model (*Salmonella* in Peanut Butter) -> Process Stage (Storage) -> Edit Note, and the feature worked as expected (screenshot 4-3).

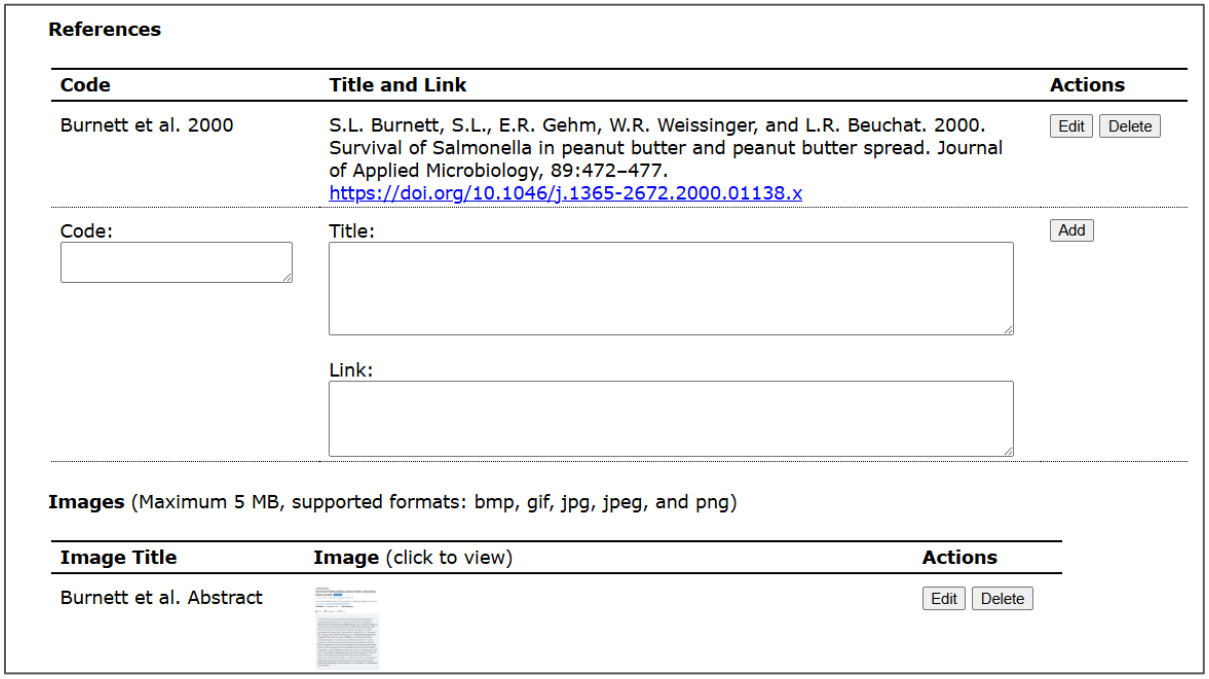
Screenshot 4-1.



Screenshot 4-2.



Screenshot 4-3.



Question 5: Comment on the FDA-iRISK 5.1 Technical Document sections relevant to the new features, with a focus on those in Groups A, B and C. Is it sufficiently clear in the description of the modeling approach, mathematical functions (where applicable), and other aspects to document the validity of the underlying model structure of FDA-iRISK? If not, please identify which aspects are unclear, and what changes should be considered to improve clarity and transparency.

The reviewers found that the FDA-iRISK 5.1i Technical Document was well-written, clear and complete, and that it sufficiently described most of the new features. The reviewers indicated that the document provides a wonderful overview of models to be used in risk assessment, except the comments noted elsewhere on the distribution warping (related to feature B3) and on the method of aggregation of chronic exposure across multiple foods (related to feature B1).

FDA Response:

We thank the reviewers for the positive comments on the technical document. Regarding a need to further explain warping, we have revised the term "warping" to "Exponential Percentile Adjustment" and clarified that this function is to provide a convenient non-linear option for exploratory analysis (see also our response to Question 2). Regarding the comments on a need to explicitly describe the method of aggregation of chronic exposure from multiple foods, see our response to Question 2.

Question 6: The Office of Management and Budget (OMB) memo M-19-15, Improving the Implementation of the Information Quality Act (https://www.whitehouse.gov/wp-content/uploads/2019/04/M-19-15.pdf), notes that information disseminated by each federal agency be fit for its intended purpose, and that each agency considers the appropriate level of quality for each of the products it disseminates based on the likely use of that information. Given the intended purpose of FDA-iRISK, please comment on the utility, integrity, and objectivity of the model in general and the specific new features specifically.

The reviewers found that the FDA-iRISK tool including the underlying model structure and algorithm is robust (albeit complex), useful, and fit for purpose. It was noted that the tool offers a lot of flexibility in functionality and that the new features increase efficiency and further enhance a "user-friendly" experience. Overall, the peer reviewers emphasized that FDA-iRISK relies on the user's technical knowledge for the completion of accurate risk assessments but also noted the reliability of the computational infrastructure provided by the tool. The reviewers commented that the tool is best implemented by expert users, or individuals with the relevant background and education necessary to understand the data, assumptions, and modeling principles inherent to risk assessment.

More specifically, the reviewers emphasized that a certain degree of relevant knowledge and education to understand FDA-iRISK is necessary to use the tool responsibly because the users are responsible for model inputs (i.e., data) and for choosing appropriate modeling options provided in FDA-iRISK. It was noted that ideally, "*a team of users with different expertise would collaborate when using iRISK, including those who understand the (principles of) modelling and those who understand the data*.".

The reviewers indicated that based on their reviews using the test cases and practical (some hypothetical) data provided by FDA, the system (computational infrastructure) demonstrated reliable and repeatable results.

The reviewers also commented that, as constructed, FDA-iRISK provides users with quite a lot of flexibility for data entry, copying, replacement, modifications, visualization, control of the degree of complexity of the assessment, etc., and the new features A, B, C and D further enhance the FDA-iRISK capacities in areas such flexibility, efficiency (data/process copying/sharing) and user-friendly interface in generating report/visual. Nevertheless, the reviewers emphasized that users of FDA-iRISK are required to provide all the data, assumptions, and knowledge about hazards and foods. One reviewer commented that this system is only suitable for expert users.

FDA Response:

We thank the peer reviewers for the positive comments about the utility, integrity, and objectivity of FDA-iRISK in general and the new features specifically. We agree with the reviewers that expert users (who are both knowledgeable about risk assessment and familiar with FDA-iRISK) can navigate the tool and use its features with ease. We have incorporated into the

Overview section of the FDA-iRISK 5.0 Technical Document (Ref. 1) the language from the reviewer regarding a team of users with different expertise who would collaborate when using the tool. We agree that training may be necessary to assist food safety professionals and other users to gain sufficient relevant background knowledge on modeling principles inherent to risk assessment, to understand data and assumptions, and to become familiar with how to navigate and use FDA-iRISK efficiently.

Overall, for FDA-iRISK users that may have a wide range of risk assessment experience and may be interested in a range of different food safety issues (e.g., microbial vs. chronic chemical), a tiered approach to training and novel approaches to delivering the logic and key aspects of the FDA-iRISK 5.0 Technical Document (Ref. 1) and the User Guide (Ref. 2) may be necessary so that new users are not overwhelmed. We plan to keep the intended users in mind in future efforts to refine FDA-iRISK and make the tool more accessible.

Question 7: Do you have comments on how the FDA-iRISK tool might be applied more broadly to support risk prioritization? Do you have any additional comments? Please share them in your review.

The reviewers were not aware of any other tool that could be applied so broadly to risk prioritization for food safety applications. They noted that FDA-iRISK is unique in that it provides an overarching approach to quantifying risks associated with microbial and chemical hazards. One reviewer indicated that specific differences in the model structure between the two types of hazards are a consequence of the difference in the nature of the hazard (microbial vs. chemical hazards), and therefore unavoidable. The reviewer stated that FDA-iRISK follows the current standards in risk assessment modeling well, and that the tool holds a very good balance between putting responsibility to the user (in terms of the question to be answered, the data used, the choice of the model, the preferred metrics) and offering support (in shape of a well-developed template for the risk assessment, including a report). Furthermore, the use of a harmonized approach (e.g., a common health metric for comparison between the risk considered for microbial and chemical hazards) is essential for risk prioritization.

Another reviewer commented that the application of FDA-iRISK in support of risk prioritization would depend on the demand and the context. The expected main use of the tool would be to support regulatory decision making in food safety, but the reviewer is unsure whether anticipated users would be mainly FDA and regional agencies in the U.S. or also international equivalents. The reviewer would encourage the use of FDA-iRISK by international agencies and noted the need for enhanced communication and guidance in the use of FDA-iRISK, especially where there are aligned objectives with other initiatives. The reviewer also suggested the creation of repositories that could be used internationally and noted such development could be challenging because it would demand a suitable infrastructure to build up and maintain the repositories. In separate comments, another reviewer suggested creating a list of “data needs” to assist users

(especially new users), since creating a risk model in FDA-iRISK requires quite a lot of data input from users.

Other comments related to the terminology "Lifetime Average Daily Dose (LADD)" used universally for chronic exposure and risk scenarios throughout the technical document. A reviewer commented that the term LADD and averaging over the lifetime is only suitable for cancer risks. For chronic non-cancer risks, the exposure windows can be less than lifetime, e.g. lead exposure during childhood, that can result in chronic health effects; in this case, the exposure is not averaged over the lifetime. The reviewer also noted that from the feature B test cases and the technical document, it is apparent that FDA-iRISK provides the capacity for users to define the durations of life stages (e.g., as the entire lifespan or for childhood) and the tool generates an average daily consumption (called LADC). This feature allows users to define the critical windows of exposures and calculate daily dose during that critical window and not lifetime. The reviewer suggested that universal use of the term "lifetime" should be clarified in the technical document, because it is confusing in scenarios where the same term refers to a window of the less than lifetime chronic exposure. The reviewer suggested that the term "Average Daily Dose/Lifetime Average Daily Dose (ADD/LADD)" be used to better describe what can be calculated.

Another reviewer provided comments that the description of the usage of the OC curve was clear in the technical document, but it did not include adequate detail on how the probability at the end of the sampling process is actually used. Specifically,

> *"Equation 29 is used per food unit. Overall, this affects the distribution of concentrations of all food units in the tested batch(es), and the prevalence. How are these adjusted distributions of concentrations and prevalence calculated? Are all batches/food products tested? It makes a difference which assumptions are made on the testing regime used. When only a fraction of baches are tested, and only some samples are taken, what happens? Or is that realistic scenario not included?*"

The reviewer also indicated the usefulness of the description regarding theoretical minimum and maximum temperatures and concurred with the necessity that FDA-iRISK defines the experimental and the theoretical temperature separately – the latter is a parameter required for some of the predictive microbiology models. The reviewer suggested that it may be worthwhile to somehow remind the user of this when working with the tool, because it is an important detail that is easily overlooked.

The reviewers also provided general comments. They indicated that the test cases and the step-by-step instructions provided for the new features are clear and very straight forward. They noted that the user guide (v4.4i September 2023) provided as a reference did not include description and explanation for the new features, which should be added later. The reviewers also found some typographical errors in the instructions, or that in some instances the name of a tab, field, hazard; or behaviors did not match instructions (added highlights and comments throughout the PDF test case documents). A reviewer commented that the FDA-iRISK tool has become very

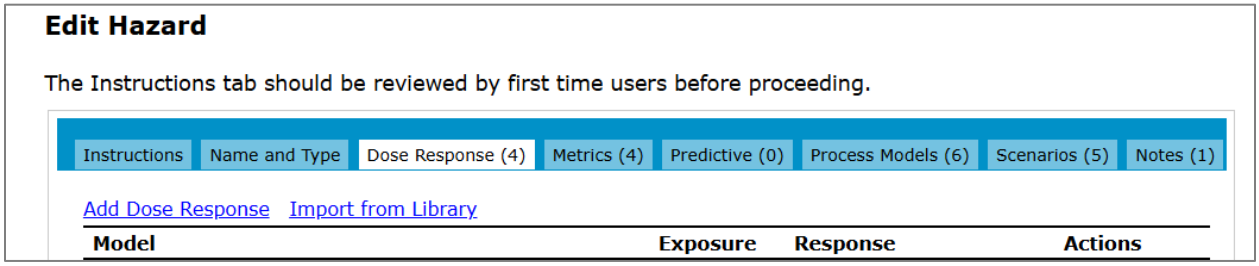
powerful and very complex, and that it has become so complex that one really must be an expert in the tool to be able to quickly navigate and use the features.

FDA Response:

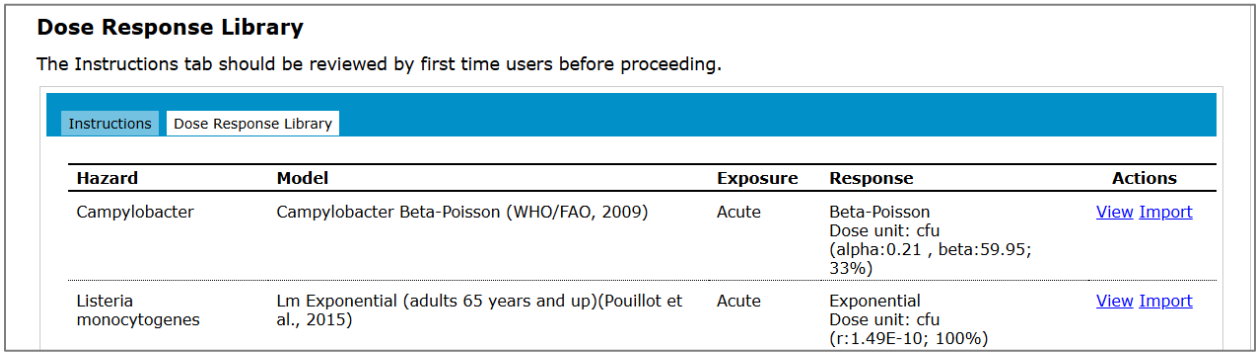
We thank the reviewers for the positive comments that FDA-iRISK is uniquely suitable to support risk prioritization in the food safety domain. As the reviewers recognized, FDA-iRISK by design can be used to quantify and compare microbial and chemical food safety risks based on a common health metric (e.g., DALY), using current standards in risk assessment modeling. In developing the tool, we have purposefully aimed for a good balance between counting on users' responsibilities and providing built-in functions and automated features that allow users to conduct fully quantitative, fully probabilistic risk assessments for microbial and chemical hazards.

We thank the reviewers for the suggestions on potentially expanding the use of the tool to inform decision making both within the U.S. and international agencies. We plan to explore ways to address this and other comments, such as finding ways to create more shared repositories, and will keep in mind some of the potential challenges. FDA-iRISK is well-designed to address the suggestion regarding the creation of "international" repositories with models that could be copied, modified, and further expanded. By using FDA-iRISK as a knowledge management system, a group of organizations or users can create and share model elements, e.g., using the Import from Library feature (screenshot 7-1) to share and import from a Dose Response Library (screenshot 7-2) or using a similar feature to import from a Consumption Model Library. They can also create and share risk scenarios and exposure scenarios, e.g., using the Copy/Import feature (screenshot 7-3). Regarding the suggestion on a list of "data needs" for building risk models, we plan to explore this as part of the efforts to find more ways to deliver the content of the FDA-iRISK 5.0 User Guide (Ref. 2).

Screenshot 7-1.



Screenshot 7-2.



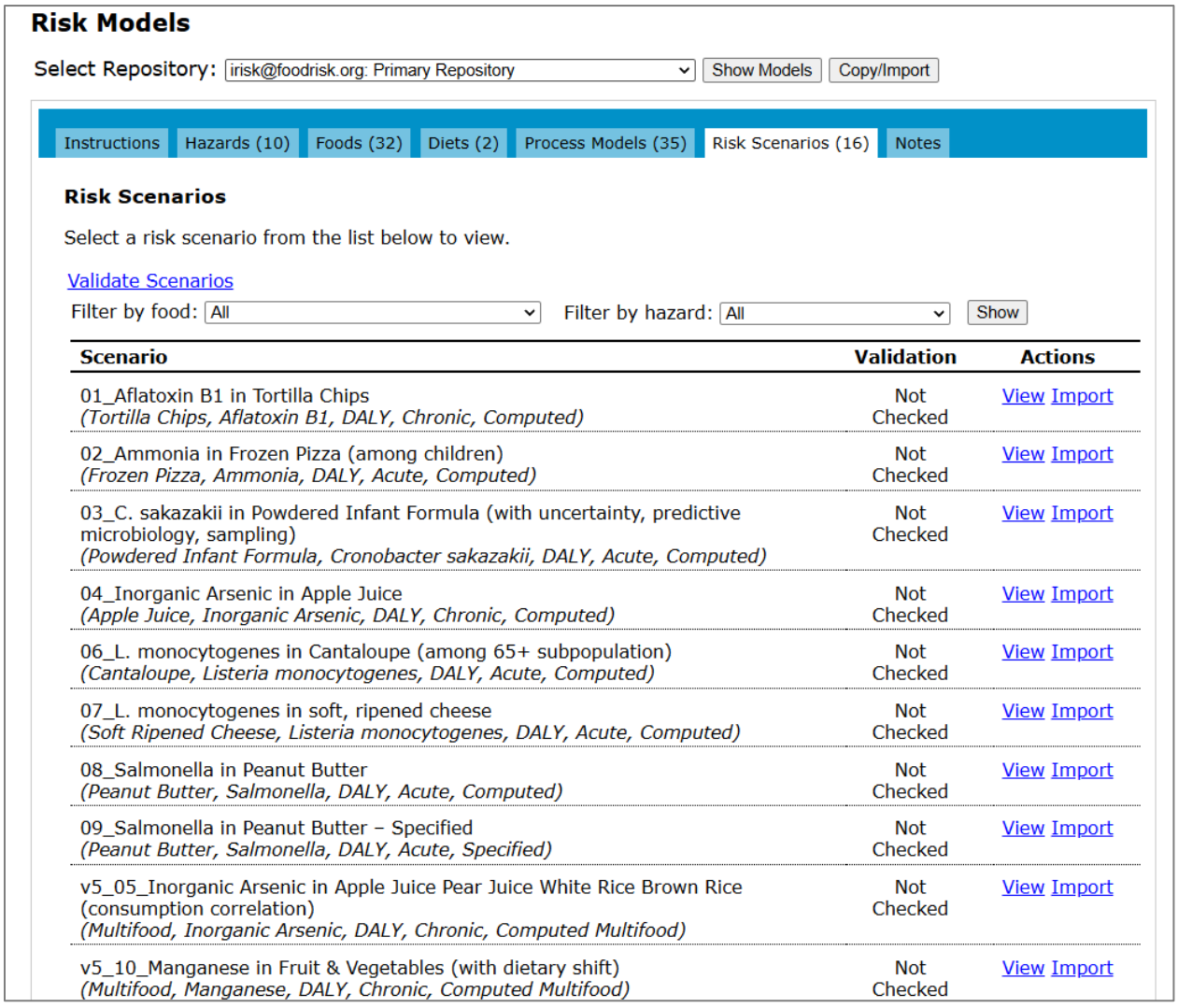
Dose Response Library

The Instructions tab should be reviewed by first time users before proceeding.

Instructions | Dose Response Library

Hazard	Model	Exposure	Response	Actions
Campylobacter	Campylobacter Beta-Poisson (WHO/FAO, 2009)	Acute	Beta-Poisson Dose unit: cfu (alpha:0.21 , beta:59.95; 33%)	View Import
Listeria monocytogenes	Lm Exponential (adults 65 years and up)(Pouillot et al., 2015)	Acute	Exponential Dose unit: cfu (r:1.49E-10; 100%)	View Import

Screenshot 7-3.



Risk Models

Select Repository: irisk@foodrisk.org: Primary Repository | Show Models | Copy/Import

Instructions | Hazards (10) | Foods (32) | Diets (2) | Process Models (35) | Risk Scenarios (16) | Notes

Risk Scenarios

Select a risk scenario from the list below to view.

Validate Scenarios

Filter by food: All Filter by hazard: All Show

Scenario	Validation	Actions
01_Aflatoxin B1 in Tortilla Chips *(Tortilla Chips, Aflatoxin B1, DALY, Chronic, Computed)*	Not Checked	View Import
02_Ammonia in Frozen Pizza (among children) *(Frozen Pizza, Ammonia, DALY, Acute, Computed)*	Not Checked	View Import
03_C. sakazakii in Powdered Infant Formula (with uncertainty, predictive microbiology, sampling) *(Powdered Infant Formula, Cronobacter sakazakii, DALY, Acute, Computed)*	Not Checked	View Import
04_Inorganic Arsenic in Apple Juice *(Apple Juice, Inorganic Arsenic, DALY, Chronic, Computed)*	Not Checked	View Import
06_L. monocytogenes in Cantaloupe (among 65+ subpopulation) *(Cantaloupe, Listeria monocytogenes, DALY, Acute, Computed)*	Not Checked	View Import
07_L. monocytogenes in soft, ripened cheese *(Soft Ripened Cheese, Listeria monocytogenes, DALY, Acute, Computed)*	Not Checked	View Import
08_Salmonella in Peanut Butter *(Peanut Butter, Salmonella, DALY, Acute, Computed)*	Not Checked	View Import
09_Salmonella in Peanut Butter – Specified *(Peanut Butter, Salmonella, DALY, Acute, Specified)*	Not Checked	View Import
v5_05_Inorganic Arsenic in Apple Juice Pear Juice White Rice Brown Rice (consumption correlation) *(Multifood, Inorganic Arsenic, DALY, Chronic, Computed Multifood)*	Not Checked	View Import
v5_10_Manganese in Fruit & Vegetables (with dietary shift) *(Multifood, Manganese, DALY, Chronic, Computed Multifood)*	Not Checked	View Import

We thank the reviewers for the comments and suggestions regarding the terms LADD and "lifetime." We have incorporated language suggested by the reviewer and added text to clarify the use of these terms in several sections in the FDA-iRISK 5.0 Technical Document (Ref. 1),

including 4.3 Chronic Exposure, 4.4.3 Calculation of Lifetime Average Daily Consumption, and 5.2 Dose Calculation, Chronic Exposure.

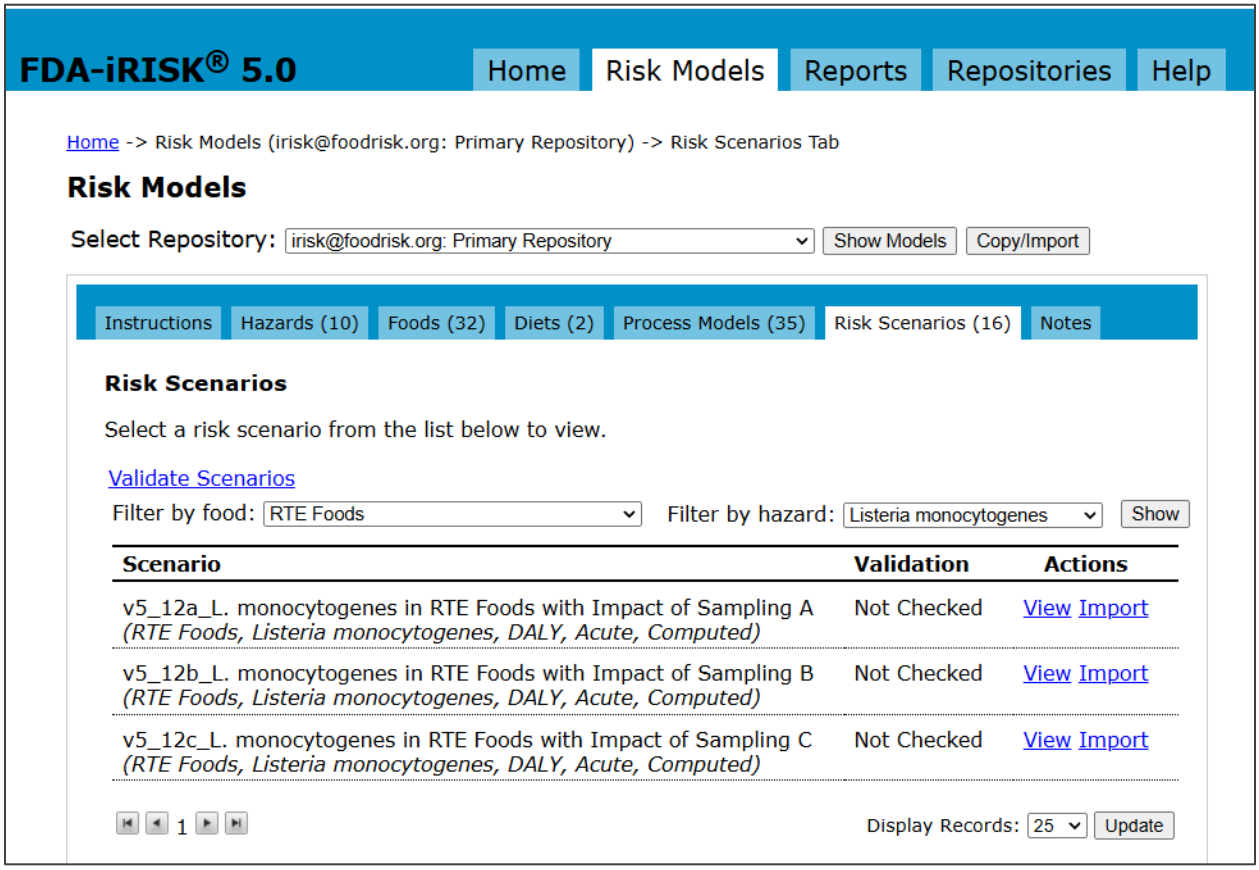
We thank the reviewers for the comments and specific questions regarding the description of the usage of the OC curve. We agree that it is important to explain how the probability at the end of the sampling step is calculated and actually used. Equation 29 is used to calculate the probability at the end of the sampling process stage ($PrevPost$) for a "food unit" as a function of three parameters: the probability of contamination in the prior process stage for the given food unit (*PrevPrior*), the proportion of food units that are tested (*Ptest*), and the performance of the sampling plan at the sampling process stage. The sampling plan performance is defined by the operating characteristic (OC) curve file the user constructs or uploads, which contains a set of data points that correspond to points on an OC curve with the y-axis representing Probability of Rejection (P_reject; or alternatively P_accept) and the x-axis representing concentration ($\log_{10}$ cfu/g) in the "food unit".

We agree with the reviewer that, overall, the Equation 29 output affects the distribution of concentrations of all food units in the tested batch(es), and the prevalence. In the context of Equation 29, "food unit" is a batch (i.e., a lot). Whenever sampling is included in the Process Model of a scenario in FDA-iRISK, the initial conditions in the Process Model represent:

(a) prevalence that is the likelihood that a lot is contaminated,
(b) concentration distribution that is the distribution of the mean concentrations of all contaminated lots in production (or in the food supply) being evaluated at the sampling process stage, and
(c) unit size that is the lot size. The sampling OC curve is generated for a sampling plan of interest (e.g., a 2-class sampling plan $n = 5$, $m = 0/25$ g, and $c = 0$) assuming a certain within-lot standard deviation (e.g., 0.8 $\log_{10}$ cfu/g) of the underlying $\log_{10}$ normal distribution with a mean that would be sampled from the concentration distribution described in (b).

More details on the relationship between within-lot characteristics and OC curve is available in the FDA-OC App (https://foodsafetyrisk.org/OC). In FDA-iRISK 5.0 released in March 2026, we shared with users several example risk scenarios (screenshot 7-4), to illustrate how a sampling OC curve is uploaded and used in a risk scenario to predict the impact of between-lot and within-lot variability in *L. monocytogenes* contamination on risk reduction from sampling ready-to-eat foods.

Screenshot 7-4.



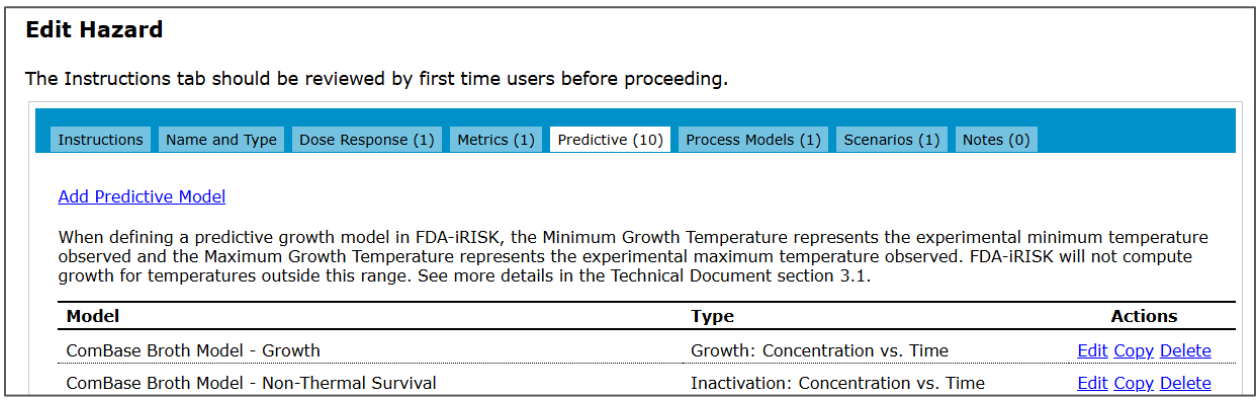
It does make a difference whether only a fraction of batches (i.e., lots) is tested and whether only some samples are taken from a lot for testing. The number of samples taken from a lot for testing (a component of a sampling plan that, for example, also includes the microbiological limit and the acceptable number of samples exceeding the microbiological limit) defines the OC curve and thus the sampling performance. The user defines the fraction of batches tested as an input (i.e., *Ptest*). These features in FDA-iRISK allow users to define realistic scenarios. The FDA-iRISK 5.0 Technical Document (Ref. 1) section 2.3.14 "Sampling (OC Curve) – Microbial" provides the following explanation for the Equation 29 parameters, how the probability of contamination at the end of the sampling process (i.e., adjusted prevalence) and adjusted distributions of concentrations are calculated and used:

> Of note, when a sampling step is implemented, the generic term "food unit" is treated as a lot in the test-and-reject process (as the Simple Poisson and OC-Curve process types are implemented). The proportion of food units tested is the proportion of lots tested. In FDA-iRISK, homogeneity of concentrations within a food unit (a lot) is assumed, and thus the initial contamination conditions include inputs for the prevalence among lots, and the distribution of the mean concentration among lots (note: there is not an option to define within lot distribution to reflect variability of concentrations within a lot).

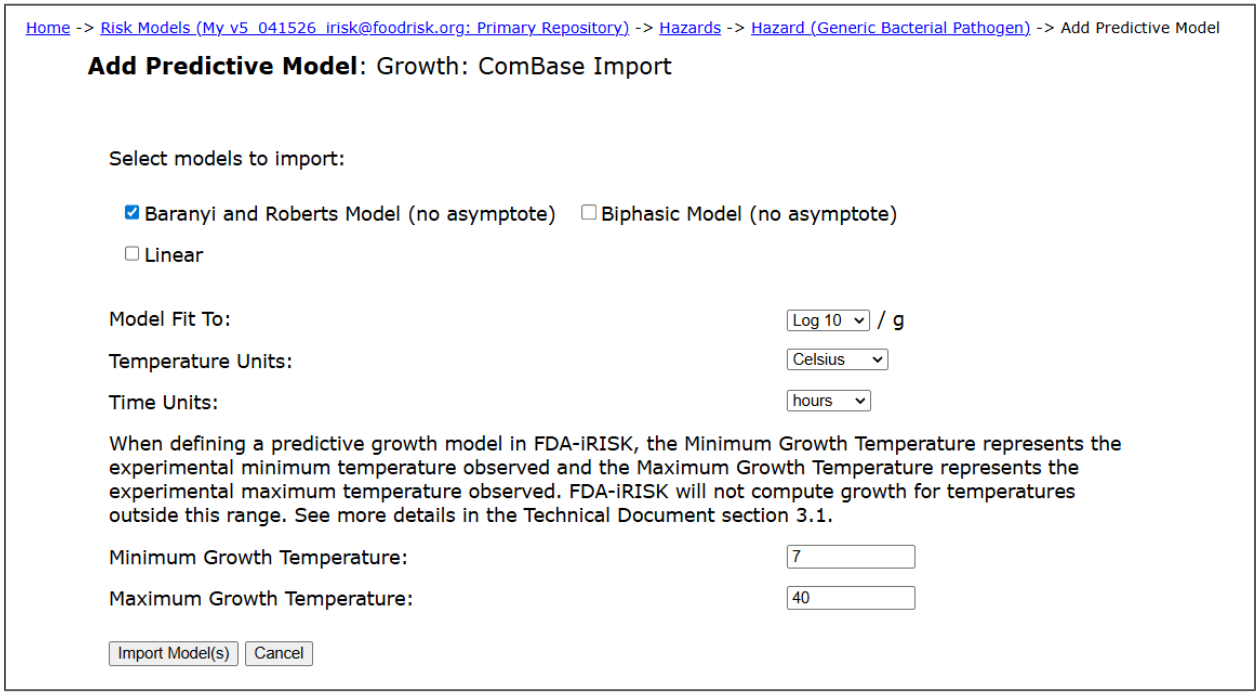
FDA-iRISK estimates the probability of rejection (for a given concentration value) and uses this probability to adjust the prevalence weights for the concentration values, essentially resulting in an adjustment in the between-lot concentration distribution. For example, contaminated "lots" will be rejected according to the performance of the sampling plan OC curve (and the most contaminated lots are more likely to be rejected). The contaminated lots rejected are "replaced" by a random lot (which may or may not be contaminated, and may or may not be tested), resulting in a decrease in the prevalence-weighted average concentration among the "surviving" lots and an overall reduction in the number of illnesses after a sampling step is implemented, given that other model inputs are not changed.

We thank the reviewer for the suggestion and agree that it is worthwhile to remind users of the detail under "Note with regard to minimum and maximum temperatures" in section 3.1 of the FDA-iRISK 5.0 Technical Document (Ref. 1), pp.42-43. To help ensure that the important details are not overlooked when users define a growth model or import a growth model from ComBase, we have updated the FDA-iRISK user interface to explain the required inputs of Minimum Temperature and Maximum Temperature and point to further details in section 3.1 of the Technical Document, as shown in screenshots 7-5 and 7-6 below.

Screenshot 7-5.



Screenshot 7-6.



We thank the reviewers for the general comments and specific suggestions. We have corrected the typographical errors and language inconsistencies in the instructions. Indeed, we have used the step-by-step instructions (revised where needed to match wording and behaviors on the user interface) for the test cases as the basis for the content for the new features, which are now included in the FDA-iRISK 5.0 User Guide (Ref. 2).

We agree with the reviewer that the FDA-iRISK tool has become very powerful and very complex, especially for new users. To make it less overwhelming, we have also provided a simpler Quick Start guide (Ref. 3), which is designed to introduce new users to the FDA-iRISK interface and lead them through the creation of several types of risk scenarios. We suggest to the users that after getting familiar with the basic features of FDA-iRISK, for more information about additional features and capacities, they can refer to the FDA-iRISK 5.0 User Guide (Ref. 2) and the FDA-iRISK 5.0 Technical Document (Ref. 1). As described in our response to Question 6, FDA-iRISK users may have a wide range of risk assessment experience and may be interested in a range of different food safety issues (e.g., microbial vs. chronic chemical). Therefore, a tiered approach to training and novel approaches to delivering the key aspects of the FDA-iRISK 5.0 Technical Document and the User Guide may be necessary. We plan to keep the intended users in mind in future efforts to refine FDA-iRISK and make the tool more accessible to help promote risk-based thinking and risk-based approaches to food safety management.

References Cited in the FDA Response:

Ref. 1.
Food and Drug Administration Human Foods Program (FDA/HFP), Joint Institute for Food Safety and Applied Nutrition (JIFSAN), and Risk Sciences International (RSI). 2026. FDA-iRISK® version 5.0. FDA/HFP. College Park, Maryland. Available at https://irisk.foodrisk.org/. FDA-iRISK® 5.0 Food Safety Modeling Tool **Technical Document**, retrieved from https://irisk.foodrisk.org/Documents/FDAiRISKTechnicalDocumentation.pdf. Accessed July 10, 2026.

Ref. 2.
Food and Drug Administration Human Foods Program (FDA/HFP), Joint Institute for Food Safety and Applied Nutrition (JIFSAN), and Risk Sciences International (RSI). 2026. FDA-iRISK® 5.0 Food Safety Modeling Tool **User Guide**, retrieved from https://irisk.foodrisk.org/Documents/FDAiRISKUserGuide.pdf. Accessed July 10, 2026.

Ref. 3.
Food and Drug Administration Human Foods Program (FDA/HFP), Joint Institute for Food Safety and Applied Nutrition (JIFSAN), and Risk Sciences International (RSI). 2026. FDA-iRISK® 5.0 Food Safety Modeling Tool **Quick Start**, retrieved from https://irisk.foodrisk.org/Documents/FDAiRISKQuickStart.pdf. Accessed July 10, 2026.