Final Comment Report

External Letter Peer Review of FDA's

FDA-iRISK 5.1 Advanced Modeling Features and Technical Document

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I. INTRODUCTION

Versar Global Solutions (Versar), an independent Food and Drug Administration (FDA) contractor, coordinated an external letter peer review of FDA-iRISK 5.1 Advanced Modeling Features and Technical Document. The peer review was conducted for FDA's Center for Food Safety and Applied Nutrition (CFSAN).

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 four peer reviews: the first in 2010, with a focus on microbial hazards; the second in 2013, with a focus on chemical hazards; and the third in 2016, with a focus on second-order simulation and other advanced features; and the fourth in 2020, with a focus on importing empirical models and parameter sets, streamlined complex sensitivity analysis, additional predictive models, and multi-institutional access to a shared instance of FDA-iRISK. Comments from the peer 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. FDA-iRISK 4.2 was made public in March 2021.

The focus of this review is on new features 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, and C5.

Versar conducted an independent search for three scientific experts where one reviewer has chemical risk assessment expertise, and two reviewers have microbial risk assessment expertise.

Peer Reviewers:

Maarten J. Nauta, PhD
Statens Serum Institute, Denmark

Nga Tran, Dr. PH, MPH
Exponent

Donald W. Schaffner, PhD
Rutgers University

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.

III. INDIVIDUAL REVIEWER COMMENTS

A. Reviewer #1

Comments on *FDA-iRISK 5.1 Advanced Modeling Features and Technical Document*

Reviewer #1

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.***

   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).

   It all seems to work correctly. It is a very nice feature that Combase results can be captured and uploaded well. My comments are "minor".

   When uploading Combase models, it would have been helpful to get an explanation of the principles behind the navigation through the iRISK tool is it is done in the testcases. 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.

   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. For example in **A3**, with A3 process model complete, in the process stage, I see I have the broth growth model and can indicate the time, but I do not see how much growth that gives in terms of log increase. I have to look that up in the model itself under the hazard tab, to find out that, for example, for 4-6 hours this is between 0.03 and 0.14 log increase. This may not be intuitive for all users. In the Report, I only see an increase from 1.62 to 1.71 log cfu, which is a bit challenging to check.

   I see the example used is the Salmonella growth model at 20°C that you get in Combase. This seems relevant information. If I were to model Salmonella, it would be nice to see the growth conditions that I used (as indicated in Combase) in my iRISK Report. But I probably have to add that as a note myself? This is not necessarily a big deal, but it would be nice for a user if the input values of a Combase model would be provided alongside the output.

   This is a more general point: the input values are provided in the Excel sheet from Combase, but seem not to be taken up by iRISK. It would be nice if the growth or inactivation conditions used are shown, either in the iRISK tool when working with it, or in the report.

   When I came to **A7**, I thought I understood the process well and made an error: 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. I struggled a bit with that. It was my own mistake of course, but I realize I would have been helped by an appropriate error message, indicating that the type of model was incorrectly selected.

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.

This comes back to what I noted above: I missed the temperature (and other inputs) in the report when a Combase model is used. The temperature is not a parameter in the Combase model that is applied, which is probably the reason for not including it. But it may be relevant for the user anyway, as an aid to understand what the process model is actually modelling.

In the exercise, 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. I do not get the point. The technical document does not help me.

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. I do not understand.

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.

I can upload the files following the instructions and see good looking OC Curves. It works appropriately.
The application of the curves does not follow from the instructions, I did not test that.

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.***

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.

B1: This is not my main expertise, but it seems reasonable to introduce the correlation, and to do it in the way it is done. So it makes sense to me.
B3: The setup and implementation are reasonable and allow the user to run the model for alternative consumption scenarios that make sense.
C2: I cannot find specific sections in the Technical Document referring to the issues in the test cases, comparing and showing risk scenarios.
C5: I see no unreasonable assumptions in the methodology

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).

B1: I see no problems.
B3: I get confused about the warping. I did not know the term and wondered what it could mean. I checked pages 70-71 in the Technical Document, but found it is not clearly explained there, or at least in technical terms but not intuitively. (I remember I understood it during the presentation, but no longer now).
Minor observation: When I played around with it in the "edit multifood life stage and consumption" page in iRISK, under the Diets tab, at some points the "modified Consumption Distribution" did not show, but I was not able to reproduce that error.

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).

The approach to model shifts in diets is understandable and seems right to me. But this is not my main expertise. 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 them. Which 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: if you stop eating one thing, you start eating something else, which has health effects as well. It will become pretty complex to take that into account.

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. But when interaction comes into play, or dose response depends on underlying (lifestyle) factors, gender or age, it gets complicated, and the approach used may no longer be valid. For that reason, I don't think the iRISK approach would be the most efficient when doing risk-benefit assessments of foods involving diets. I would say we don't know what approach to take for that purpose anyway.

We once wrote a review paper indicating issues in risk benefit assessment: Nauta et al. 2018 Meeting the challenges in the development of risk-benefit assessment of foods. **Trends in Food Science and Nutrition** 76:90-100. https://doi.org/10.1016/j.tifs.2018.04.004

When performing the C5 test case I ran into two issues:
1) in Test 2 step 6, there is a big jump in the tool from diet to Food 1. 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.

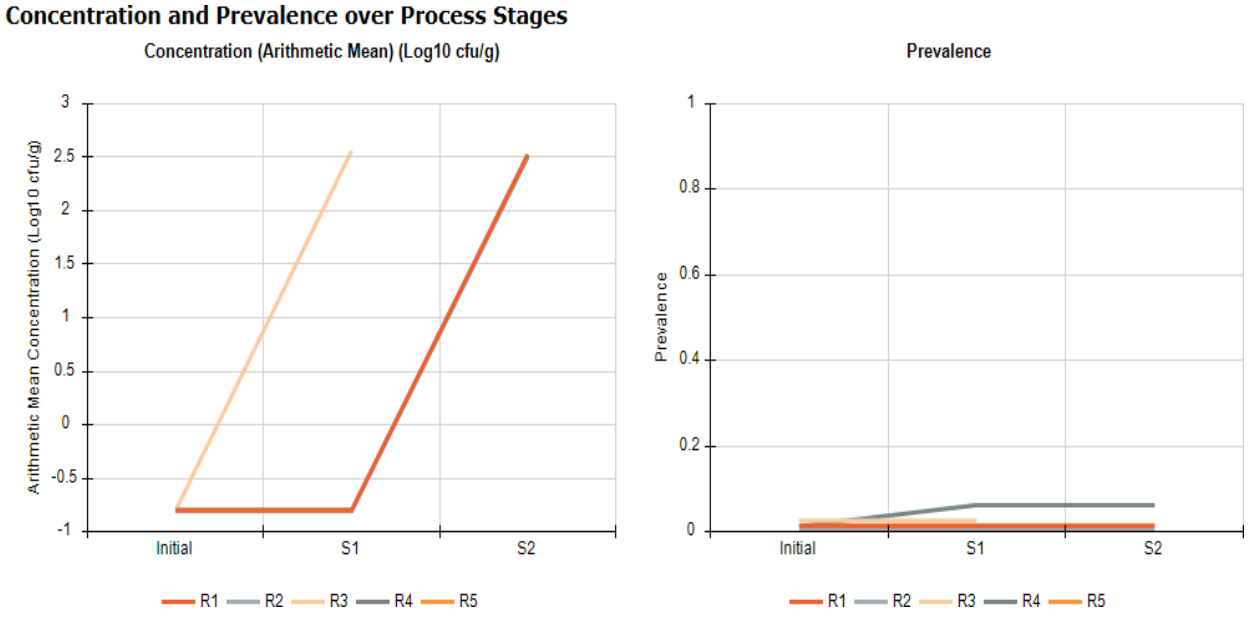
2) I do not understand the difference between "C5 No diet" and the "C5 Diet baseline". I see no difference between the two, and this surprised me. They are both presented under different names, suggesting that there is a difference. But I do not understand what this difference is. Why is the distinction made in the first place? The 14000 DALY estimated in the baseline for C5 Diet, are not found for C5 Diet in the report. This is not clear to me. 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.

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

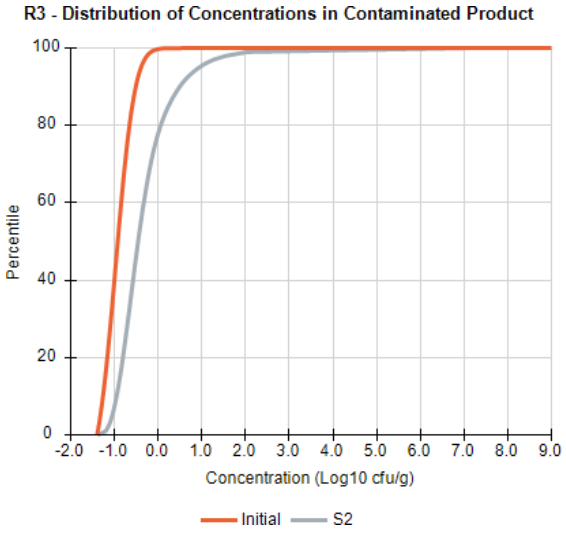
3a. Are these features adequate for the intended purpose? If not, please explain what changes might be considered and how they would improve the feature(s).

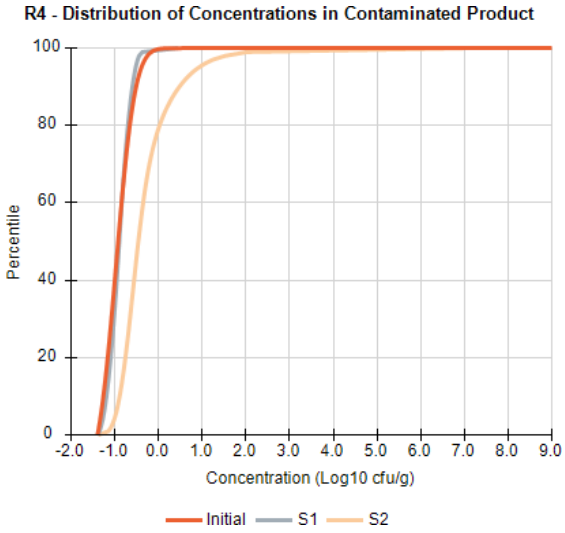
C1 (C2_a): It all seems to work as intended and is well implemented.
I struggle with the line graphs for "Concentration and Prevalence over Process Stages".

- 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.
- 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. See below.



Yet, it calls it S2 in the graph with distributions of stages for the scenario R3. See below.





The same happens in C_2e.

C3: Seems to do what it should. The report produced probably includes all the information needed, but it is quite hard to comprehend for a human being. Maybe I do not know very well what to look at as this is not my specific area...
Just an idea: it may be possible that a Language Model (AI) helps to interrogate the report and pick out what is of interest for the reader. But that is for iRISK 6 :-).

C4: I get a bit lost in the logic here. I understand it is useful to re-use existing models, and this seems to work well. However, it is challenging to get the important details when reading the reports. It may be clear when we understand well what you are doing (which is in general advisable ;-)) but unfortunately these multifood models are unusual to me, and the complexity may be confusing for more users.

I note 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.

I repeated Test case “8 Test Cases for C4”, Test 1, and had a little challenge with the process models no longer showing “TBD”, as I still had them from the last time, and didn’t know how to put them back on TBD (steps 6 and 10). But then I still had my old reports.

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.

After re-doing the test, I believe that 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.

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 test case shows how prepared files can be imported and shows clear error messages when there are errors in the Excel files. I could not find a description of how the import files should be provided in Excel, but I guess that on the basis of the examples you can quite easily construct them yourself as a user.

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

See above. Sorry if I mixed up answers and questions.

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?

I went through the test cases and it all works smoothly. For users familiar with the underlying question and the approach, it is user friendly.

Two remarks:

D3, test2: When you copy a process model 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 (?).

D3. test3: what exactly is done with the food and hazard when you click the "use existing hazard" and "use existing food" options are not clear to me. 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? The issue is then that you can copy the process model but not the same hazard and food as in the original repository, as you already have them (and maybe defined differently). The test case does not show whether this is the issue and how it is solved. Therefore, I am puzzled.

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 technical Document is well written, clear and complete, a wonderful overview of models to be used in risk assessment.

B3: I do not think the warping is well explained, Table 4_9 does not help me.

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.

To answer this question, the intended purpose and the anticipated users should be known. The Technical Document describes the users as knowledgeable about the hazards, foods and processes. I would expect that 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. Using iRISK outside that context would be rather irresponsible: you have to know what you are doing.

In that context, I believe iRISK is very useful and fit-for-purpose. You need some time to understand the logic, but that makes sense: you cannot do this kind of work without some relevant background knowledge and education.

There is no reason to doubt the integrity or objectivity of the tool. The input (i.e data and models used) is the responsibility of the user, the tool uses algorithms for which integrity and objectivity are not an issue.

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.

I am not aware of any other tool that can be applied so broadly to support risk prioritization in the domain of Food Safety, by applying a highly similar approach for microbial and chemical food safety risks. The differences in approach between the two are a consequence of the difference in the nature of microbial and chemical hazards, and therefore unavoidable. It follows the current standards in risk assessment modelling well. I think it 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). Besides, the usage of a harmonized approach (between the risk considered) is essential for risk prioritization.

The application of the tool for support in risk prioritization will depend on the demand and the context. I expect that the main usage of the tool would be to support regulatory decision making in the area of food safety, but I am unsure whether foreseen users would be mainly FDA and regional agencies in the US, or also international equivalents. I would encourage the latter, but it would require enhanced communication and guidance in the use of FDA-iRisk, and maybe line- up with other initiatives. Building repositories that can be used internationally would be great, but also demand a suitable infrastructure to build up and maintain them. Which will be challenging.

II. Specific Observations on FDA-iRISK 5.1 Advanced Modeling Features

General comments: The guidance through the test cases that you provided is very straight, so clear that when going through I was tempted to forget to think about what I was actually doing. I assume the document refers to the technical document, and not the user guide, which does not seem to be updated. The User Guide version provided is for version 4.4.i sept 2023. I expect the User Guide is the guide that user will refer to first, it should also include the description and explanation of the new features. I assume this will be added later.

Page	Paragraph/Line	Comment
30-31	2.3.14	The description of the usage of the OC curve is clear but does not detail how the probability at the end of the sampling process is actually used. Eq. 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?
43-44	1132-1151	It may be worthwhile to somehow remind the user of this when working with the tool. It is an important detail that is easily overlooked.

B. Reviewer #2

Comments on *FDA-iRISK 5.1 Advanced Modeling Features and Technical Document*

Reviewer #2

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.***

   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).

   No major comments. I found a typographical error in the instructions. I found that the name of a tab, field, hazard, or behaviors did not match instructions.

   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.

   Unclear when temperature is not defined, it's just that there's no mention of temperature.

   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.

   No comments.

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.***

   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.

   No group B features reviewed.

   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).

   No comments.

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).

Not reviewed.

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

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).

Some feedback has been provided regarding the clarity of the instructions for C1

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.

Not reviewed.

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

No comments.

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?

I noted a lack of clarity regarding importing a shared repository throughout the exercises. I made a specific comment in the group D features document. I was never able to get the image import functionality to work correctly. I've provided comments in the documents.

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.

No comments.

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.

No comments.

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.

No comments.

II. Specific Observations on FDA-iRISK 5.1 Advanced Modeling Features

I've added highlights and comments throughout the PDF test case documents.

The iRISK tool has become very powerful and very complex. It has become so complex that one really has to be an expert in the tool to be able to quickly navigate and use the features. This review exercise for me became an exercise in whether I could follow the directions and understand how to use the tool, and less about evaluating the technical correctness of the tool.

C. Reviewer #3

Comments on *FDA-iRISK 5.1 Advanced Modeling Features and Technical Document*

Reviewer #3

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.***

   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).

   Group A features relate to microbiological risk assessments and not my area of expertise. No comment.

   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.

   Group A features relate to microbiological risk assessments and not my area of expertise. No comment.

   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.

   Group A features relate to microbiological risk assessments and not my area of expertise. No comment.

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.***

   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.

   The assumption associated with the methodologies for the B1, B3, C2, and C5 are reasonable and consistent with modelling practices. The model provides users with flexibility to modify underlying assumptions and data input and generate good data visualizations.

   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).

B1 features focus on the food consumption aspects of the model, mainly allowing users to account for correlation of food consumption between life stages and between foods. 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 method of aggregation of chronic exposure from all foods that are being assessed under the Multifoods/singe hazard and Multifoods/multiple hazards is not explicitly described in the Technical Document. The only description is on page 58 and Figure 4 of technical document, which states the following:

"FDA-iRISK introduces the concept of multifood chronic scenarios in which the exposure from multiple food sources is aggregated to compute a LADD over all food types prior to applying the dose-response model to compute the mean risk of illness per consumer. A multifood scenario is otherwise very similar to a single food scenario (see Figure 4)."

Based on this description and Figure 4 of the technical document, it is assumed that the aggregation in the iRISK model is a sum of exposure across all foods that are under consideration in a Multifoods scenario. It should be 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.

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).

B3 features (modify diets) and C5 are related. The test case could be more efficient with collapsing these two test sections into one.

The diet modification options provided, i.e. based on simply changing the percent consumers and/or shifting the consumption distribution, is useful for hypothetical "what if" assessments, particularly in cases where there is a risk/benefit trade off (e.g. methylmercury vs omega-3 in fish). However, it is noted that, while the model may work well for a single food single hazard, it is not evidently clear scenarios involving multiple foods (for example pesticides vs phytonutrients in fruits and vegetables) can be implemented. The potential for overestimation in aggregating across foods (see above) is more of an issue with nutrients, since the concern here is under (not enough nutrient, shortfalls) and not over (exceedance). Further, in nutrient assessment, usual intake is used, so users should be made aware of data need when attempting nutrient assessment.

Comment on C5 – Test 1:
Add diet – can only one food at a time, is it possible to select multiple foods in the drop-down menu?
Diet shift – shifting percent consumer only is logical.
For scaling, there are linear and warping options – what is the basis for these options?

C5 test 2. Test that users create a diet with the new structure – create report step is confusing. How does user navigate w/out step by step instruction as in the test case?

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

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).

Overall, these features are adequate for their intended purpose.

B2 features of importing ort chronic multifold consumption models works well. The test cases provided were easy to follow.
C1 features relate to micro hazard and not my area of expertise so I did not review.
C3 features add sensitivity analysis to Multifoods, Multihazard scenario and relates to consumption correlation. Test case provided were easy to follow. However, the generating of report when there are multiple foods/hazards was slow.
C4 – Multifoods with pre-run processed model for concentration (single hazard) –
Test 1. Test that users run process models associated with a multifood scenario and access stored results -- test fine, no issue.
Test 2. Test that process models are only run when their parameters are modified for sensitivity analysis when scenario set to use existing process model results-- test fine, no issue.
This new feature of pre-run processed model is good improvement in efficiency.

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.

B2-import chronic multifold consumption models – test case works fine.
Feature B2 test case demonstrates the functionality well and there is no issue.

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

Yes, the test cases provided are adequate to demonstrate the functionality of the new features. See above comments.

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 copying of hazard, foods and process models into current and different repositories is user-friendly.
D1:
Test 1 – Test that the user can copy a hazard to the same repository – ok easy to copy
Test 2 – Test that the user can copy a hazard to a different repository – ok easy to copy
D2:
Task 1 – Copy to own repository – foods – ok
Test 2 – Test that the user can copy a food to a different repository – ok
D3:
Test 1 – Copy a process model to the same repository – ok
Test 2 – Copy a process model to a new repository - ok
Test 3 – Copy a process model to a new repository using an existing same hazard and food – ok
D4-a:
Test 1 – Create, edit and delete note references – ok
Test 2 – Test that the note references show in the report – ok
D4-b:
Test 1 – Create, edit and delete note images - ok
Test 2 – Test that the note image shows in the report – ok
D5:
Test 1 – Test that process model details can be excluded for sensitivity analysis sets - ok

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.

No comments on A.

For B and C features, the technical document sufficiently described the new features, model approach and mathematical function, except for the aggregation across multiple foods (see comment on B1 features above).

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.

Overall, FDA-iRISK model is robustly complex, including seven elements: the food, the hazard, the population of consumers, a process pathway (i.e., food production, processing and handling practices), consumption patterns in the population, dose response relationships, and burden of

disease measures associated with health effects. The main concept behind the design of FDA-iRISK is the reliability associated with the computational infrastructure, when combined with the user's technical knowledge, will ensure higher quality and more productive risk assessment activity. Based on the test cases and hypothetical data provided in this review, the system (computational infrastructure) demonstrated reliable and repeatable results.

As constructed iRISK allows users with quite a lot of flexibility for data entry, copying, replacement, modifications, visualization, control of the degree of complexity of the assessment, etc. The new features (B, C and D) tested in this review demonstrate the flexibility and some increase in efficiency (data/process copying/sharing) and user-friendly interface in generating report/visual. Nevertheless, as users of FDA-iRISK are required to provide all of the data, assumptions, and knowledge about hazards and foods, this system is only suitable for expert users.

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.

For chronic exposure, the terminology lifetime average daily dose (LADD) is used universally, and the technical report (page 57) states: "In a risk scenario for chronic exposure, the consumption model is used to generate a value for the average amount of the food consumed per day (on a per unit body weight basis) over a lifetime of exposure." It should be noted 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 lead to chronic health effects. In non-cancer chronic risks, we do not average the exposure over the lifetime.

Based on description in the technical document (Equation 47), technical document lines 1272-1275 (page 60) and review of the feature B tests on food consumption and e life-stages, the model's generated average daily consumption (called LADC) appears to be based on the durations of the life stages as defined by users. This is a great feature as it allows users to define the critical windows of exposures and calculate daily dose during that critical window and not lifetime. The universal use of the term "lifetime" in the less than lifetime chronic exposure is confusing and should be clarified. It is suggested that the term "ADD/LADD" is used to better describe what can be calculated.

Since the model requires quite a lot of data input from user, it would be helpful to have a list of data needed for users who wish to use the model.

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No comments provided.