108. Comment:

Page 17 – Scope and Mandate – The three risk management questions: I question whether "impact" is the correct way to evaluate the risk assessment. As I feel impact looks beyond just what the number is but also at economical and regulatory effects. Therefore, I am reviewing the document more from the standpoint of whether all aspects where taken into consideration to develop a useful risk assessment tool for policy decisions.

108. Response:

No response is necessary.

108. Comment:

Page 18, lines 40-47, Page 19, lines 1-11 – Discussion is given about temperature abuse and that the majority of poisonings are not linked to RTE products produced in FSIS facilities. Therefore, if we look at a policy impact by changing cooling/stabilization requirements in FSIS plants will we have a public health impact since regulatory authority is limited in restaurants or institutions. This needs to be addressed maybe more in the Policy Context on page 19.

109. Response:

The purpose of the risk assessment is to evaluate what would be the effect of changes in regulations on growth, not to pre-suppose that there would be no effect, as the reviewer appears to imply. The section on Policy Context is not present to comment on policies, but simply to place the assessment in context, so we have not changed the text.

110. Comment:

Page 21, lines 17-23 – Is there any data on the number of CP outbreaks linked to partially cooked foods? Also, do we have any data that shows the links to products produced from FSIS inspected facilities? My question then becomes what link from a foodborne illness standpoint can we make to RTE and partially cooked products produced in FSIS facilities. Are they doing their job at controlling CP during heat and cooling?

110. Response:

Between 1990 and 1999, no *C. perfringens* outbreaks with identified etiology and vehicle have been reported as linked to partially cooked food (in the regulatory sense), but 1 of 153 has been linked to an RTE product (Section 2.2 — we have added the qualifiers as to etiology, vehicle, and time frame to the text). However, it should be recognized that most outbreaks are not reported, nor is the etiology or vehicle always determined in those that are reported. Commenting on "doing their job" is not within the scope of this risk assessment.

111. Comment:

Page 22, Figure 2.1 – Do we have any indication of why the numbers were greater in 1998 and 1999 and what the products were?

111. Response:

We have not evaluated these questions, since they lie outside the scope of the risk assessment. The source data for these figures is readily available, as cited.

112. Comment:

Page 22, line 5 – Needs to be moved closer to Figure 2.2 and would be better as a footnote.

112. Response:

We do not understand the reviewer's concern, since this line immediately preceded Figure 2.2 on the page, and is the only text line referring to Figure 2.2 (so should not be a footnote). We have removed one extraneous blank line between the cited line and Figure 2.2, but left the line in the text.

110. Comment:

Page 24, lines 11-12 (typo – delete space between 24 and %) and Figure 2.7 – The statement and graph indicate that USDA-regulated food products were responsible for 76% of total *C. perfringens* while 24% of the food sources are unknown. However, previous data mentions that it is not linked to product produced in these plants. My concern then are CP outbreaks linked to raw meat and poultry that are processed in FSIS facilities but the CP outbreak is really due to improper refrigeration during transport, cooking, holding, or cooling by the consumer or food service operation. This information is critical for determining FSIS's role in the regulatory process for setting CP stabilization standards.

113. Response:

The typo has been corrected. This risk assessment is solely concerned with RTE and partially cooked products, so we have not investigated the reviewer's concerns about other products. Questions about FSIS's role in the regulatory process are also outside the scope of the risk assessment.

114. Comment:

<u>Exposure assessment</u>

The exposure assessment is outlined very logically and includes the various steps in processing, transporting, and re-heating RTE and partially cooked meat and poultry products.

114. Response:

No response is necessary.

115. Comment:

Page 29, lines 5-7 – Processing - more steps should be added to include what is in Figure 3.1. Initially when I read these lines I thought that the initial steps and primary heating steps had not been included. Therefore, this added information would be helpful.

115. Response:

In addition to the modification of the description of Figure 3.1 (see Response 20) we have added explicit reference to Figure 3.1 in each of the steps, so that there can be no confusion. The three branches at the bottom of Figure 3.1 are now explained under the heading "Preparation (reheating)."

116. Comment:

Page 30, Figure 3.1 – Under re-heated, the option of X-ed and spores activated probably needs to be added as another potential option since veg. cells die is an option on this side. Many re-heating steps will more than likely cause complete killing of veg cells and also spores could be activated.

116. Response:

The figure accurately shows what is done in the calculations and has not been changed. The possibility of complete killing of vegetative cells is already inherent in the calculation (and in the description of Figure 3.1). While it is quite possible that this re-heating would activate spores, the assumption here is that the food would be eaten before they have time to germinate. This immediate consumption has been made clear under the heading "Preparation (reheating)" in the short summary of the steps included in the risk assessment.

117. Comment:

Page 34, lines 8-15 – More explanation is needed in this section to explain the food categories and explain foods that were also omitted from the model and how the omitted foods would be considered from a stabilization standpoint and also in regards to risk assessment.

117. Response:

The explanation the reviewer requests is already present in Appendix A, as explained in Response 106. We have modified the text to make this clear. See also Response 178.

118. Comment:

Page 35, Table 3.1 – More explanation is needed in this table. In Food Category 1 under characteristics could the initial or final ppm of nitrite be included or defined as a range. Also, define or give a range of times and temperatures for hold holding. Under Reasoning, it would be

helpful to define highest risk process as related to CP and when the risk occurs during cooling at the manufacturer or during reheating or lack of reheating.

118. Response:

It is not possible to give specific ranges for nitrite concentrations, since they are not known. Appendix A describes fully how nitrite was taken into account, and we have added statements in that Appendix that document that CSFII data can be used to infer salt content of servings (from sodium concentrations) but do not contain information on nitrite concentrations. At the time Table 3.1 was constructed, it was not known what was the "highest risk process as related to CP and when the risk occurs during cooling at the manufacturer or during reheating or lack of reheating" — that is one piece of information the risk assessment could be used to throw some light on, if necessary. However, such considerations did not go into the reasoning behind Table 3.1, so should not be listed there.

119. Comment:

Under Category 3 – It would be helpful to have a definition/footnote in regards to the abcd letters. Another concern is that some of the products may also be used in a food service operation and possible can be hot-held. Under Characteristics and Reasoning, an actual pH range in the BBQ product would be helpful.

119. Response:

We are not sure what information the reviewer wishes to see in the footnotes, since all available information is already provided in the table. The entries in Table 3.1 are descriptive, and were used only descriptively, since the information about food servings in CSFII is descriptive only. As we state in Section 3.4, in the introduction to Table 3.1, foods categories were "further separated according to likely characteristics relevant for estimation of numbers of *C. perfringens* vegetative cells in the food as eaten, using example foods as a guide." Thus we cannot provide actual pH ranges, since we do not have that information, nor was it used in categorizing food servings. As indicated in Table 3.1, all that can be done in these categorizations is to indicate the likely fate of food servings, not determine them with certainty. It is not possible to determine whether particular food servings in the CSFII (to which these categorizations were applied) with certainty, so we cannot be sure which foods are hot-held, or what fraction of foods likely to be hot-held were in fact hot-held.

120. Comment:

Under Category 4 – The pH range would be helpful under characteristics. It would also be helpful to have a range of times and temperatures for hot holding for 4acd.

120. Response:

As above (see Response 119), we do not have such information. The categorizations were based on descriptions only, not on measurements.

121. Comment:

Page 36, lines 36-38 – Needs to be a little more clear in regards to the salt content.

121. Response:

We have added the phrase "assuming all sodium is from sodium chloride" to state exactly what was done.

122. Comment:

Page 37, lines 8-9 – More explanation is needed to explain what is meant by a heat treatment, are you referring to steam pasteurization, steam vacuuming or even an acid rinse that would occur at a slaughter plant. If so have any studies looked at the reduction of CP in meat due to the above intervention strategies?

122. Response:

We are referring to the heat treatment required as a lethality step for raw meat used in RTE foods (and all the RTE foods included in the risk assessment are treated with such a heat step). The reviewer appears to be confusing this with surface cleaning steps applied to meat possibly for other purposes. To clarify, we have changed "likely kills all vegetative" with "is intended to kill all vegetative," to emphasize that the lethality step is referred to. There are many studies that have examined the reduction in CP in meat due to such interventions, but these are irrelevant to the risk assessment since the lethality step is not in question.

123. Comment:

Page 37, lines 39-44 – The USDA/FSIS baseline survey looked at incidence rate of CP in raw products and did not focus on heat treatments, this is slightly unclear when the heat treatment is mentioned. Also, did Hall and Angelotti show a high or low initial level of CP in products?

123. Response:

We have tried to remove any ambiguity about the USDA/FSIS baseline survey by stating "including a heat step in the analysis method" in place of just "including a heat step." As stated, Hall and Angelotti did not enumerate CP, so we do not know the levels. The method they used could have detected one cell in their 25 gram sample, but it was entirely a yes/no procedure. If the reviewer is referring to the prevalence they found, that is shown in Table 3.2.

124. Comment:

Page 38 – It would be helpful to add text to explain why the other three studies were chosen and what data was able to used to help with the model. One concern is that the studies have higher initial end point temperatures and it is hard to determine if any "come-up" times were also taken into account. Many RTE meat and poultry products have staged thermal processing schedules/cycles that would allow for additional lethality or even potential outgrowth. Was this taken into account?

124. Response:

The other three studies were chosen because they were all that remained to provide information, and their design appeared adequate to provide the information required. We have modified "Six studies were evaluated" to "Six studies were located and evaluated" to indicate the limited pool of studies available. We are not sure of the comparison point when the reviewer states "the studies have higher initial end point temperatures." The studies are those that give us information on the spore content of the raw meat products; we require that the initial lethality step be sufficient for effectively complete killing of vegetative cells.

As previously stated, the initial lethality step is not at issue; all vegetative cells are assumed to be killed during the lethality step in processing meat for RTE foods. It is not clear whether the reviewer is referring to additional lethality and potential outgrowth of vegetative cells originally present in the meat, or derived from spores that germinate somewhere in the process. If the former, we are not interested in those vegetative cells at this point, since they are killed at some subsequent time. If the latter, the additional lethality/outgrowth is considered part of the "growth during stabilization" term in the model.

125. Comment:

Page 39 – In the Greenberg study, it is good that samples of meat were available but a 3 gram sample size is slightly limiting considering mostly 25 g samples are currently taken. Was the small sample size taken into consideration in regards to potential false negatives?

125. Response:

The Greenberg study was used only qualitatively, to obtain the shape of the concentration distribution particularly at high concentrations. The detection limit (which depends on the meat sample size) is practically irrelevant for this purpose. However, it should be noted that the 3 gram sample size referred to is the quantity that was cultured (and this convention is adopted throughout the text), not the meat sample size initially taken. This quantity cultured is unusually large, so that the detection limit was unusually low in the Greenburg study (as stated in the text). While 25 gram samples of meat may be initially taken, the whole 25 grams

is not cultured. In all the literature examined, some small sub-sample, usually in the range 0.1 to 1 gram, was ultimately cultured.

126. Comment:

Page 40, Figure 3.2 - More information is needed to explain the figure better such as number of samples of what type of product (raw, heat treated, meat, poultry, hot dogs) were samples ground, whole muscle…Also should it be number of colonies per 3 g sample or per gram, what is the unit.

126. Response:

The reviewer appears to be misconstruing the purpose of Figure 3.2. Its purpose is not to convey the concentrations observed in Greenburg *et al.* 1966, nor in what products (both of which are adequately described in the cited reference, and, in fact, in Table 3.2 and the text), but simply to illustrate the adequacy of fitting a gamma distribution to the upper tail of the concentration distribution For this purpose the material requested by the reviewer is irrelevant, indeed misleading, since we are showing a comparison of the observed and predicted frequency of counts (pure numbers); it does not matter in what the counts occurred (they could in principle have been in samples of different sizes, for example). We have therefore added the phrase "illustrating the adequacy of fit of a gamma distribution" to the caption.

127. Comment:

Page 40, 3.4.3 – In the studies it would be helpful to explain the samples as related to the heating parameters to determine links between meat and poultry cooking cycles.

127. Response:

We have added the phrase "prior to the sampling and analysis" at the end of the sentence "All three studies included heat steps corresponding closely to those expected for RTE foods" to clarify this point.

128. Comment:

Page 42, Table 3.4 – The parameters of the heat treatments for the different products would be helpful to add to the footnotes.

128. Response:

The heat treatment used was the same for all products and was described in Section 3.5.3. We have added the sentence "In all cases the same procedure was applied to all samples" there to make the common heat treatment clear.

129. Comment:

Page 43, lines 6-10 – Although, the studies give estimates at fairly high heat processing temperatures, more research is needed to explain different processing schedules and addressing integrated lethality and how this may have an effect on the numbers.

129. Response:

The reviewer appears to be confusing the stabilization step in the model with the heat treatment step. While these two may be intertwined in actual practice, the model treats them separately. We have added the phrase "(that is, post heat treatment but prior to stabilization)" after "the data of Kalinowski *et al*. (2003), Taormina *et al*. (2003), and Eblen *et al.* (2004) were used to estimate the initial levels" in an attempt to make this clear.

130. Comment:

Page 44, lines – I have a concern that the cured and uncured data was mixed together as cured products have both salt and nitrite and these products were excluded in the model. I would consider maybe just dropping the cured and would agree with keeping everything together as the range may also represent variability of CP from plants and due to varying thermal process schedules.

130. Response:

Taormina et al. (2003) specifies which results are from cured meats and which are from uncured meats. Most of the raw meat samples used in this study have been cured in an unspecified way. However, normal curing methods are not expected to affect unactivated and ungerminated spores. The cured raw meat samples were diluted 10-fold in peptone water, stomached, and filtered to produce a homogenate that was cooked, so the concentrations of any curing agents present in the cooked homogenate samples would be unlikely to affect activation and germination of spores. Finally, the results of Taormina *et al*. were used only as an upper bound on the estimates of concentrations, since Taormina *et al*. did not confirm presumptive *C. perfringens* colonies. We therefore do not share the misgivings of the reviewer, and the analysis has not been changed.

131. Comment:

Page 45, Figure 3.3 – More explanation is needed and should also at least indicate CFU/g of meat and poultry? Also why is USDA/FSIS included instead of Eblen (is this a mistake). The USDA/FSIS data does not include heating steps.

131. Response:

We have added the phrase "concentrations in meat and poultry" to the end of the caption. The reviewer does not specify what further information is missing from the explanation, and we are at a loss to know. We have corrected the notation

USDA/FSIS to Eblen *et al*. (Eblen *et al*. are with USDA/FSIS, and the original document had a different citation involving USDA/FSIS).

132. Comment:

Page 46, lines 26-28 – It would be helpful to put the prevalence in servings based also on a typical serving size of meat and then to an entrée or to at least give the number of ounces = 100 grams.

132. Response:

We have added the sentence "The weighted average quantity of meat per serving evaluated in this risk assessment is 69.5 grams (2.45 oz.); the prevalence in servings with that quantity of meat is about 1.30%."

133. Comment:

Page 47, 3.6.1 – Examples of partially cooked products would be helpful. The upper range temperature is also needed. This information would aid in better determining if the prevalence and levels of *C. perfringens* in partially cooked products should be the same as identified in raw meat products.

133. Response:

As stated in Table 3.1, the only food codes in the CSFII database that could be identified as partially cooked were chicken patties (see also Appendix B, where all the food codes are listed). We have added a cross-reference back to Table 3.1. We do not know the upper temperature range, nor is it as helpful as the reviewer suggests because partial cooking may involve temperature gradients throughout the product.

134. Comment:

Page 51, lines 12-14 – Relate serving size back to ounces and then give an example of how much of a serving may be needed to make a person sick.

134. Response:

The conversion to ounces has been added. It is not possible to state "how much of a serving may be needed to make a person sick," since that would also depend on both the concentration within the serving (which concentration varies from serving to serving) and the strain of *C. perfringens* involved (which also varies from serving to serving). Moreover, at best only a probability value could be specified, not a definite statement as to whether someone would or would not get sick. At this point in the discussion, we also believe that any attempt to make such a statement would be out of place, since dose-response is not evaluated until Section 5. We have therefore not included any such attempt here.

135. Comment:

Page 53 – I am concerned that many of the studies related to spices are fairly old and that spices are treated much differently to control pathogens. Is there any information on treatment of spices in regards to current manufacturing practices? I feel that this is somewhat covered better in section 3.7.3

135. Response:

We share the reviewer's concern, which is why Section 7 (Research Needs) contains the recommendation to investigate current type A, CPE positive *C. perfringens* spore concentrations in spices. We did not locate published information, other than those referenced, on any relationship between *C. perfringens* concentrations and treatment of spices, or that evaluated the current prevalence of various treatments. The cited page reference was a discussion of available studies, while the cited section (now Section 3.8.3) discusses how the analyses of as-measured concentrations are used in the risk assessment, so the coverage is appropriate.

136. Comment:

Page 54 – I agree that it is best to combine the spices as for the most part, industry generally as spice companies create blends for specific products. However, may need to state the potential for over or under estimating due to the actual spices in a specific product.

136. Response:

Section 4 explicitly includes a statement to this effect, namely that "Combination of spices into the groups selected here adequately represents the spice concentrations in diverse spices."

137. Comment:

Page 59, lines 29-39 – Please include the actual water activity values.

137. Response:

Only qualitative information is required at this point, so a forward reference to Section 3.11.5.5 has been added, since the same experiments are discussed there in more detail with this quantitative information.

138. Comment:

Page 61, lines 33-37 – I'm a little concerned that only one study related to heat sensitive/resistant strains involved meat and the data showed a large fraction of spores germinating. Is the data adequate to really analyze strain differences and germination rates?

138. Response:

As indicated in Section 3.9.4 discussing the use of the results the reviewer cites, and in the Research Needs of Section 7, we share the concerns of the reviewer. The data are not adequate to analyze these differences, so we made a best estimate and used sensitivity analysis.

139. Comment:

Page 66, line 20 – Delete extra .

139. Response:

The stray period has been deleted.

140. Comment:

Page 75, Table 3.24 – More explanation of the table is needed. A footnote explaining the mathematical symbols would be good for both Table 3.24 and Table 3.23.

140. Response:

The mathematical symbols are explained in Sections 3.11.1 and 3.11.2, and a note has been added to that effect immediately following each of the tables cited. Equation 3.21 has been clarified by adding the definition of the symbol f to equation 3.15. It takes two full sections to adequately explain all the symbols, so footnotes for this purpose are impractical. The general methodology used for obtaining the tables has been explained in the added Section 3.3

141. Comment:

Page 76, lines 1-6 – Explain why this data was evaluated and also indicate that the storage temperatures are not at all typical for many meat products.

141. Response:

We have renamed Section 3.11 to "The growth of *C. perfringens* and *C. botulinum*" and modified the sub-sections accordingly, with an explanation in Section 3.11.1 that the growth of *C. botulinum* is required to respond to one of the original questions posed (see Section 1.1). The temperatures cited by the reviewer relate to growth of *C. botulinum*, not to storage temperatures, and commenting on storage temperatures here (in a section entirely on growth rates as functions of temperature and other parameters) is inappropriate.

142. Comment:

Page 76, Figure 3.4 – Similar comments as were addressed in the Executive Summary. Hard to determine treatments in the graph and was the *C. botulinum* in a specific meat or poultry product.

142. Response:

See Responses 16 and 25.

143. Comment:

Page 80, lines 19-21 – May want to also include statement that many RTE products are also cooked in casings or packages that also provides an anaerobic environment.

143. Response:

This information has been incorporated.

144. Comment:

Page 81, lines 32-38 – Is the uncertainty standard error now lower for products containing nitrite and salt compared to those with only low levels of salt as in the other Categories?

144. Response:

No. The discussion cited by the reviewer obtains an estimate of 0.582 ± 0.042 for the relative growth rate in the presence of nitrite. This relative factor (with its uncertainty) is applied to the growth rate estimated in the absence of nitrite (including its uncertainty). The phrase "This factor will be applied to all Category 1 foods" has been modified to "This factor is applied to the estimated growth rates of *C. perfringens* in all Category 1 foods" to make this clearer.

145. Comment:

Page 81, lines 42-43 – Explain the effect in more detail, increase or decrease and by approximately how much.

145. Response:

We have replaced the description with: "In their study, Juneja *et al.* (1996b, see Section 3.11.5.2) evaluated the effect of salt, temperature, sodium pyrophosphate, and pH in a laboratory broth medium. Salt appeared to be significant in various interaction terms in a model for lag phase duration (estimated from fitting Gompertz curves to experimental growth data)." As stated in Section 3.11.5.3, "the application of these results to RTE and partially cooked foods is questionable," so we did not pursue the analysis any further. In particular, we did not perform an analysis similar to that in Section 3.11.5.2, precisely because of the large disparity in lag phase durations between the broth medium measurements and the durations seen in cooked meat media. We also did not attempt to evaluate the sizes of the effect in the broth medium; attempting to use the model coefficients provided by Juneja *et al*. gave results that we considered meaningless at zero sodium pyrophosphate concentration.

146. Comment:

Page 83, lines 6-28 – I have a concern that pH can't be addressed. What about products such as fermented sausages that have low pHs below 5.0, are they less of a risk from CP because of the pH, salt and nitrite levels? Also, how do you explain the reasoning for risk in the BBQ products that potentially are more acidic? Maybe pH doesn't effect the delay phase but what about overall growth? The low pH may also be a factor in why products with higher salt and nitrite were excluded from the risk assessment.

146. Response:

Products such as fermented sausage would be considered shelf-stable (see Table A-3) because they are dried, retorted, or jar-packed, and omitted from consideration in this risk assessment as described in Section A.3.4. We noted that all BBQ sauces, tomato pastes and a number of other sauces supplied to manufacturers have rather consistent pH values (3.6-4.3) but the amount of these sauces used with various meat products is quite variable.

The relevant sentence of Section 3.11.5.4 has been modified to "An analysis of their published estimates of exponential growth rates (see Section 3.11.5.2) showed no significant effect of *pH*" to clarify where we document our analysis of the Juneja *et al*. (1996b) data showing no significant effect of *pH* on growth rates during the exponential phase. Products with higher salt and nitrite concentrations were specifically excluded from the risk assessment because they do not support *C. perfringens* growth, see Section A.3.6.

147. Comment:

Page 84 – Water Activity – I would agree with the assumption on water activity, it overall has little effect and most meat products still have fairly high water activity levels. Another factor that has been associated with water is the moisture-to-protein ratio in fermented products and jerky. This was also thought to be another safety hurdle. Research on *E. coli* O157:H7 has showed that even if the MPR is lower *E. coli* O157:H7 can still survive. Is there any research that shows a similar trend with CP.

147. Response:

Shelf-stable foods like fermented products and jerky were excluded from the risk assessment because they do not support *C. perfringens* growth, see Section A.3.4. We have therefore not investigated moisture-to-protein ratio in such foods. Survival of *C. perfringens* vegetative cells in such foods would not be important, so long as there is no growth; and spores are almost certain to survive.

148. Comment:

Page 85 – Maximum vegetative cell density – The studies need to be explained more to determine whether they were studies where inoculation of meat was purposefully done and these

were the levels that were obtained on just raw meat. It is hard to determine when the counts were taken and how is the cured aspect taken into account.

148. Response:

The descriptions of the experiments are given in the locations referenced (Sections 3.11.2 and 3.11.3). These descriptions have been enhanced to indicate the use of inoculated media, and the selection of appropriate times for analysis of counts. The "cured aspect" has no effect on the analyses, but some account was taken of this in the selection of the most appropriate estimates of growth rates (Section 3.11.3 and 3.11.4)

149. Comment:

Page 85, line 32 – Explain…and chilled (possibly twice), give an example.

149. Response:

The phrase has been replaced by "and has been stabilized"

150. Comment:

Page 87, lines 2-4 – Explain where this information came from and what are some of the parameters for cooling and stabilization. Also include examples where products such as processed meats are cold showered.

150. Response:

The phrase has been changed to "several hour" from "six hour." We have no surveys of information on cooling and stabilization parameters. We have added a parenthetical phrase "(although more rapid cooling processes are in use in some cases)" to take account of the reviewer's concern.

151. Comment:

Page 87, line 8 – delete second that

151. Response:

It has been deleted.

152. Comment:

Page 87, line 15-17 – I disagree that blast freezing should not be considered as important for products in Category 3. For food entrees and items such as chicken patties, blast freezing or individually quick frozen techniques are utilized for most of these products. These methods provide excellent stabilization and as measured by some of the research may also provide a method for killing CP cells. If this is taken into consideration, these products are much less at risk for outgrowth over 1-log during stabilization.

152. Response:

We do not deny that blast freezing or individually quick frozen techniques are excellent for stabilization. We agree with the reviewer that such methods "may" also provide a method for killing CP cells. What we accurately state is that the relationship between available research and the techniques used in industry is not clear; and we were unable to model the effect of industry techniques. This is clearly indicated in Section 4, Limitations of the Exposure Model. The overall effect of incorporating any effect for some Category 3 foods would be negligible, since the predicted fraction of illnesses due to Category 3 foods is so small (see Table 6.3).

153. Comment:

Page 87, line 40 – Check on the type of product "ground cured whole-muscle ham"

153. Response:

The description is correct. Taormina *et al*. (2003) state that the material referred to as "whole-muscle ham" was raw whole-muscle ham that was cured then ground prior to inoculation with *C. perfringens* for their experiments.

154. Comment:

Page 88, lines 14-29 – The two studies by Juneja are slightly unclear and more explanation is needed.

154. Response:

We cannot discern what aspects of these summaries the reviewer finds unclear, or what we have omitted, since they are practically identical to the other summary descriptions also provided. We have not altered them, since the summaries provide all the information we consider necessary. The cited original studies may be examined for more details, and our analysis is provided in the workbook CP_cold_storage.xls accompanying the risk assessment.

155. Comment:

Page 90, Table 3.29 – Explain "decades/day"

155. Response:

See Response 28

156. Comment:

Page 93, Lines 2-9 – These values are slightly higher than normal refrigeration and more explanation is needed in regards to how they fit into the model.

156. Response:

The temperatures mentioned do not correspond to storage temperatures, but to temperatures at which growth of *C. perfringens* vegetative cells has or has not been observed. The paragraph has been slightly re-phrased to make this clearer.

157. Comment:

Page 105, Figure 3.15 – Change the lines if not printing in color.

157. Response:

We have examined all the figures in the document, and changed them so that color is not the only distinguishing feature between any lines on them. In addition, we have attempted to ensure better clarity in the captions.

158. Comment:

Page 106, Figure 3.16 – Change patterns of lines or indicate by pointing to lines.

158. Response:

See Response 157.

159. Comment:

Page 107, lines 21-30 – Microwave cooking and even oven cooking will have variability and many times what may happen is that a person will heat a product and the middle will be slightly colder and then upon mixing have a fairly uniform product but from a microbial standpoint heating was not uniform. Might want to figure out a way to address this situation.

159. Response:

We agree. Heating patterns are likely to be complex for both oven and microwave heating, and we have also neglected the time between heating and consumption. We have modified the paragraph to indicate this, and also added a comment that the low sensitivity of the results to heating times suggests that such effects are probably not important for the risk assessment.

160. Comment:

Page 110, Figure 3.19 – The legend for Cat. 4c is hard to read.

160. Response:

See Response 157.

161. Comment:

Page 123, lines 20-25 – It is mentioned that the parameter values are with fixed temperatures. Is there any way that the model will take into consideration staged cooking cycles?

161. Response:

The reviewer is referred to the following section (Section A3.2.5) where the extension to varying temperatures is examined.

162. Comment:

Page 129, line 42 – Please explain the sentence "Only doses higher than 10^8 cells were administered. How does this relate to per serving size or the measurement of cells per g or ml?

162. Response:

The cited sentence is in a paragraph describing the available studies on human health effects caused experimentally by administering doses of *C. perfringens*. It is not related to serving size or measurements of cells per g or per ml., but is purely descriptive of the human experiments. We have modified and extended the sentence to read, "In these human feeding studies, all the administered doses were higher than 10^8 cells, so the effect of smaller doses must be conjectural."

163. Comment:

Page 134, 5.2.2 – How do these studies relate to food and what may be the significance?

163. Response:

We have changed the introductory paragraph to Section 5.2.2 to clarify the reasons for discussing these studies. It now reads, "As mentioned in Section 5.2.1, data from four studies were included in dose-response modeling. However, some of the six studies identified also included data acquired by administering strains of *C. perfringens* which are not expected to cause disease, or that were otherwise unusable in dose-response modeling. The reasons for excluding human feeding data from such studies discussed in the following paragraphs." Given the few human studies available, we believe it is necessary to document why some were excluded from the analysis.

164. Comment:

Page 136, lines 9-18 – Explain in regards to serving size and sickness and what is the CFU/g or mL.

164. Response:

We do not understand the reviewer's concern. We discuss here the theoretical possibility for a *single* bacterial cell to cause illness. Serving size and CFU/g are thus irrelevant to this discussion.

165. Comment:

Page 136, lines 40-46 – Do most studies show that outbreaks are linked to usually one strain?

165. Response:

The reviewer brings up a point that we investigated but did not document in the risk assessment; however it is sufficiently important that it should be documented. We have assumed throughout the risk assessment that illnesses are caused essentially by monoclones, or (probably) by closely related clones, since all the growth models are essentially of growth from monclonal cultures and the dose-response models are for single clones (this assumption is documented in Section 5.4 on assumptions about the dose-response curve). We assume that illnesses are the result of clonal growth in individual servings. There are a few recent studies that address this issue by comparison of the relationship of more than one isolate taken from foods and/or patients involved in outbreaks. A short discussion of this point has been added to the Hazard Characterization section, citing the papers involved (Ridell *et al*. 1998, Lukinmaa *et al*. 2002, and Miwa *et al*. 1999), and a reference back to that section has been added at the location cited by the reviewer.

166. Comment:

Page 141, Figure 5.3 – Change lines if not being able to print in color.

166. Response:

See Response 157.

167. Comment:

Page 142, lines 20-27 – Is there anyway to address the potential difference between broth versus meat in regards to infecting a person and the potential to get foodborne illness?

167. Response:

As noted in footnote 70, it was not possible to discern any effect of medium of administration in the available data. Such an effect may nevertheless exist, which is why we included the possibility in the list of assumptions (Section 4).

168. Comment:

Page 147, line 5 – delete a at the end

168. Response:

This typo has been corrected.

169. Comment:

Page 150, Figure 6.4 – Explain this figure more and what food Categories are taken into account.

169. Response:

The figure is explained in Section 6.3.3 (preceding the figure). We have added slightly to that explanation to try to make it clearer, and have added a footnote to indicate that, although all categories of foods are included in the simulations, the number of illnesses simulated is too small to obtain a reliable breakdown by category.

170. Comment:

Page 150, line 10 – Should this number be in degrees Celsius since other temperatures are?

170. Response:

We have mostly used °C throughout the text, but switched to °F here because the original measurements were recorded and reported in °F. The same is true for Figure 6.5.

171. Comment:

Page 151, 6.4 – How will the policy ultimately relate to public health? Do we have a good estimation of what RTE and partially cooked products are solely produced in FSIS facilities and if the policy will address only control by FSIS will the numbers truly increase? The risk model addresses stabilization for all situations of RTE and partially cooked foods and I can't get a clear understanding of the focus on the situation for FSIS inspected and regulated RTE products.

171. Response:

The reviewer's questions here all relate to policy decisions. However, the risk assessment is not concerned with policy. It does not discuss or put forward any policy viewpoints, nor is policy supposed to be discussed anywhere within it. Section 6.4 is purely a response to questions posed. It is thus not surprising that the reviewer cannot get a clear understanding of FSIS policies, since these are not addressed in the risk assessment.

172. Comment:

Page 152, 6.4.2 – More information is needed in regards to any predictions, what about looking even at *C. sporogenes* for additional trends as they relate to *C. botulinum*. It is still reasonable to state that overall control and an adequate process will have an impact on various pathogens.

172. Response:

We have not examined *C. sporogenes* and make no predictions whatever about that organism; nor was any such prediction within the remit of this risk assessment. With regard to *C. botulinum*, we have strictly answered the question posed, and not attempted to speculate about factors that we have not investigated.

173. Comment:

Page 158, 6.6.8 – Explain more the type of oven.

173. Response:

No specific type of oven is discussed; indeed "oven" versus "microwave" is used as a convenient synonym for slow versus rapid heating, without or with heat shock respectively (see Section 3.14.1). The dichotomy between oven types has been slightly re-written throughout the assessment to emphasize that the real dichotomy is between heating rates.

174. Comment:

Page 159, 6.6.11 – Is there a potential for products in Category 3 to be hot-held?

174. Response:

There is the potential for some servings that are placed in Category 3 to have been hot held. The categorization of servings, and their treatment in the risk assessment, is necessarily incomplete (since we do not have survey information on how the servings were actually prepared). The object of the categorization was to place servings in their most likely category, in an attempt to adequately evaluate different food handling methods (see Section 4, Limitations of the Exposure Model). We used criteria of product design and package size. We reasoned that single serving frozen meals, designed to be heated and served, would not be as likely to be hot-held as a large family or restaurant sized casserole pan of product such as roast beef slices in gravy.

175. Comment:

Page 160, lines 33-35 – Unclear in regards to the 1% value and how it is used.

175. Response:

The cited lines have been corrected to state that 1% of food servings placed in categories 1 and 4 were assumed to be hot-held, and Section 3.15.2 has been corrected to include category 1 as well as category 4. Also, to ease the reader's burden, cross references back to the relevant section of the document have been added to all the entries in the list of Section 7.

176. Comment:

Page 161, 5. – I question the approach used to determine this number and needed more information about the experiments to get a better idea of how the data was used/analyzed.

176. Response:

See Response 62. Also, to ease the reader's burden, cross references back to the relevant section of the document have been added to all the entries in the list of Section 7.

177. Comment:

Page 161, lines 44-45 – Should pork also be included?

177. Response:

The sentence has been corrected to replace "beef" with "meat."

178. Comment:

Appendix A

Overall, it wasn't until I read Appendix A that I realized that various products containing high salt levels, low pHs, low water activities, and nitrites were excluded from the risk assessment. This information needs to be in the Executive Summary. There as been some controversy over whether various products like those mentioned above need to closely follow Appendix B cooling guidelines. This information also needs to be included in the discussion about the various Categories in the main document and would be good to include in the Table to at least state that the various products were not considered at risk for CP outgrowth and were excluded from the model. It is also important to note that foods that are sold raw or uncooked were excluded from consideration. However, it is unsure that these products were not somehow considered from a public health standpoint where problems of CP are due to improper heating, cooling and hot-holding of meat and poultry products in food service or at home.

178. Response:

The executive summary has been augmented, augmenting the sentence "This is done using a computer program to perform Monte Carlo simulations" with ". . . on meat-containing food servings selected from the Continuing Survey of Food Intakes by Individuals (CSFII) (USDA, 2000). The selection of servings was

made to limit analysis to those servings considered capable of supporting growth of *C. perfringens* (omitting, for example, shelf-stable foods and foods high in salt and nitrite)."

The risk assessment does not enter any policy discussions, for example "over whether various products like those mentioned above need to closely follow Appendix B cooling guidelines"; the policy context is adequately discussed in Section 1.2.2.

A summary of the Appendix A procedures for selecting foods has been added at the beginning of Section 3.4, including a description of the exclusion criteria (including the exclusion of raw foods).

We agree that raw foods may be important from a public health viewpoint, but this risk assessment is solely for RTE and partially cooked foods, so raw foods are not considered anywhere here.

179. Comment:

Page 180, Table A-3 – Under Sausage, change to fermented/direct acidified. Under Slim Jim include fermented. Under Stick may be better to state Snick Sticks and include fermented/direct acidified.

179. Response:

No changes have been made to Table A-3. This lists the search terms that were actually used to locate potential foods for exclusion. The term "acidified" does not occur in any descriptor of included foods, so including "direct acidified" would not alter the outcome. "Slim Jim" is all-inclusive; any sub-headings is identified. The search term "Stick" would locate "Snick Sticks."

Reviewer Number 4

180. Comment:

Peer Review Evaluation Criteria for the *C. perfringens* Risk Assessment

1. Evaluate whether the *C. perfringens* risk assessment answered the specific FSIS risk management questions.
   a,b. The assessment properly answered the probability of human illness if allowable growth of *C. perfringens* is raised from 1 or 2 log. However the error factors are vast (Fig. E5-1). Considering the types of foods involved for this assessment and the fact these types are rarely involved in *C. perfringens* outbreaks (Table 3.1) due to inherent "hurdles" (curing salts, heating step) it is reasonable to conclude that the "errors" in practice would reflect the best-case scenario, i.e., fewer illnesses/million servings than the central estimates shown (Fig E5-1)

180. Response:

We agree with the reviewer's conclusion. We have in several places been conservative, in the sense of overestimating risks. We believe we have identified these places in Section 4 and Section 7.

181. Comment:

c. It is not possible to extrapolate to *C. botulinum* for reasons given in the assessment. Further foodborne disease outbreaks due to *C. botulinum* Type A and B are not commonly associated with the types of foods addressed by this Assessment.

181. Response:

No response is necessary

182. Comment:

2. Identification of data and critical evaluation of evidence: The authors have identified the prevalence and key characteristics of *C. perfringens* including enterotoxigenicity of isolates from foodborne disease outbreaks. One omitted study (Applied and Environmental Microbiology vol. 69, pg 1642, 2003) indicated the absence of enterotoxin-positive isolates from a variety (131) of food samples examined (forty non-enterotoxigenic C. perfringens isolates were obtained)

182. Response:

The cited study (Lin, Y-T., and Labbe, R. 2003. *Applied and Environmental Microbiology*, 69(3)1642–1646), examined 133 retail food samples from Western Massachusetts, finding 39 samples with between 3 and 292 CFU/g *C. perfringens* vegetative cells, and one further sample with >1,100 CFU/g. 85 of the samples (with 29 positive for *C. perfringens* vegetative cells) were meat or poultry

products, and a further 20 samples (with 5 positive for *C. perfringens* vegetative cells) were instant soups and dry seasonings (the remainder were fish and vegetables, so not relevant to the risk assessment). None of the *C. perfringens* detected were positive for the *cpe* gene. It was not specified whether the meat samples were raw, cooked, or otherwise processed, although by implication the meat and poultry was probably raw.

The prevalence and concentration results of this study are not directly usable in the risk assessment, since we were concerned with concentrations of *C. perfringens* vegetative cells and spores in raw meats entering processing plants for RTE and partially cooked foods, not in retail stores; and there are potentially different opportunities for contamination at the two types of location. Moreover, the geographic coverage of this study is limited (and the time frame is not specified). However, the prevalence and concentrations of vegetative cells appear similar to those in the studies examined (Table 3.8), although we have not attempted a formal analysis. The instant soup and dry seasoning results cannot be used in the risk assessment, or even compared with the values used in the risk assessment, without knowledge of the number of each type tested (only the sum is presented).

The absence of *cpe* gene in all samples tested might be usable to refine the estimate of the fraction of *C. perfringens* that are type A, CPE-positive in food samples. However, the observed fraction of *cpe*-positive isolates (0/29 for meat and poultry products; 0/5 for instant soups and seasonings) is consistent with the results used in the risk assessment (Table 3.19), and the added information would be low because of the small number of isolates. We have not added these results to the analysis, because the small information gain is outweighed by the effort involved.

183. Comment:

7. The risks have been appropriately characterized.

183. Response:

No response is necessary.

184. Comment:

10. The report clearly communicated the important issues.

184. Response:

No response is necessary.

Reviewer Number 5

185. Comment:

Review of "A Risk Assessment for Clostridium Perfringens in Ready-to-Eat and Partially Cooked Foods"

The peer review evaluation critera for the study on "A Risk Assessment for Clostridium Perfringens in Ready-to-Eat and Partially Cooked Foods" include the following:

1) Evaluate whether the C. perfringens risk assessment answered the specific FSIS risk managements questions:
   a. What is the impact on the probability of human illness if the allowable growth of *C. perfringens* is raised from 1-$\log_{10}$ during stabilization to 2-$\log_{10}$?
   b. What is the impact on the probability of human illness if the allowable growth of *C. perfringens* is raised from 1-$\log_{10}$ during stabilization to 3-$\log_{10}$?
   c. What would the relative growth of C. botulinum (relative to the growth of C. perfringens) be for each of these stabilization standards?

2) Identification of data and critical evaluation of evidence
   a. Have all key studies and data been identified?
   b. Have the data been correctly interpreted and emphasized?
   c. Please address the validity and appropriateness of all input data in the model.

3) Overreaching logical structure of the risk assessment.

4) Biological plausibility of the assumptions.

5) Are the mechanics of the model consistent with known biology?

6) Review and analysis of model:
   a. Appropriateness of modeling techniques (model mathematics and equations)
   b. Example the methodologies used in the risk assessment for estimating parameters from the data
   c. Examine/check the data analyses (spreadsheets) for compliance with the methods and overall accuracy
   d. Examine/check the source code for overall accuracy

7) Have the risks been appropriately characterized?

8) Does the risk assessment identify and characterize the following:

a. Key sources of variability and uncertainty
b. Critical assumptions
c. Important data gaps

9) User-friendliness of the model: Is the model documentation adequate to allow individuals to conduct "what-if" calculations and alter sensitivity parameters?

10) Clarity of risk assessment report: Has the report been written and presented in such a way to clearly communicate the important issues, how they were resolved, and the results?

The main focus of this review is on the following criteria: 1, 3, 6a, 6b, 7, 8, and 10. Criteria 2 is not a main focus of this review because the reviewer is not an expert in C. perfringens, and therefore is not in a position to comment on whether there might be studies or data that were not identified by the authors. However, some comment is provided on aspects of this criterion. Criteria 4 and 5 were not included in this review because the reviewer is not a biologist. Criteria 6c, 6d and 9 were not addressed mainly because of lack of adequate time given the short time frame to provide comments. For example, the time required to examine line-by-line computer code was beyond the time resource available. Moreover, the authors could report on the results of efforts to verify the model and the computer implementation of the model. Some comments along these lines are given in the following.

185. Response:

We have not specifically attempted to verify the model. Unfortunately, the data to do so do not currently exist, and their existence would, to some extent, negate the necessity for modeling — such data would include measurements of *C. perfringens* concentrations in foods during and after processing, and as it is transported from manufacturer to retailer to consumer. All the information that we could locate has been used to estimate parameters of the models, and we have attempted to list critical assumptions of the modeling in Section 4 (for the exposure modeling) and Section 5.4 (for the dose-response modeling).

Verification of the computer implementation of the model has also been very limited. We are relatively certain that the computer model does what we intended, since the code is written in highly modular form using pre-tested modules where possible, and we have tracked and verified the computations on individual servings throughout the model during debugging activities. The code for selecting servings[4] was checked by counting the result of selecting approximately 100 billion servings, and performing a chi-squared test for comparison with the expected numbers. Almost all other distributions are standard distributions, which have been individually tested. During this process, we updated some of our code for these distributions to use the fastest

[4] This uses binary search in the cumulative frequency table for servings, but each search is speeded up by pre-selecting a limited range for each search (this occurs during initialization of the program). The speed-up is by a factor of about two.

implementations that we could locate in the literature.[5] The underlying 64-bit linear congruential pseudo-random number generator is not the best now available, but was retained since it appears to be adequate for the task.[6]

To improve the possibility of others locating errors, our entire source code is included along with the risk assessment.

186. Comment:

Criteria 1: Does the risk assessment answer the specific FSIS risk management questions?

The report clearly states, on page 17 in Section 1.1, the three FSIS risk management questions. In Section 6.4, the first two of these questions are clearly answered. The analysis is highly responsive to and focused upon the first two risk management questions. Despite the complexity of the model, the answers to the risk management questions are relatively easy to summarize, especially in response to the first two questions as is done in Section 6.4.1.

186. Response:

No response is necessary.

187. Comment:

In addition to the quantitative answers to the questions, the report discusses qualitative factors that could lead to biases in the estimates, such as abusive hot-holding. It would be helpful if the authors would make a post-hoc estimate of uncertainty that takes these considerations into account, if at all possible.

187. Response:

See Response 233, where this specific comment is addressed.

188. Comment:

The authors argue that the third risk management question cannot be answered based only on information regarding C. perfringens, since estimation of growth of C. botulinum is not directly proportion and requires additional information. The rationale for not providing a more detailed answer to the third risk management question appears to be compelling, implying perhaps the need for more resources to adequately deal with this question, since a perhaps similar or parallel assessment of C. botulinum would likely be required.

[5] Speed is essential in this code, and various speed-up techniques have been applied throughout. The number of simulations required is unusually large for such simulations, because of the low incidence of illnesses.

[6] In particular, the cycle length is adequate to prevent repetition even for the hundreds of billions of servings simulated in the uncertainty analysis.

188. Response:

See Response 3.

189. Comment:

The authors perform a useful assessment of "what-if" issues pertaining to spoilage organisms and detection of spoilage by consumers. Thus, although some of the difficult to model or unmodeled factors might imply a higher risk estimate, consumer detection of spoilage and discarding of spoiled food would argue for a lower risk estimate. The "what-if" analysis requires assumptions, of course, and the assumption of the probability to dispose of food servings as a function of temperature appears to be highly speculative in its specific quantitative estimates, although intuitive plausible in terms of the general trend. The authors might comment on the plausibility of the assumption they make in this regard. Could similar "what-if" analyses be conducted for the issues raised in Section 6.4.1 pertaining to abusive hot-holding and the probable bias in reporting?

189. Response:

The reviewer is correct, and we have added the following cautionary paragraph to Section 6.5.2: "We emphasize that Equation (6.3) is almost completely speculative, and is used solely for this "what-if" analysis. No reliance should be placed on the particular shape of this curve, since only at the upper end (around 8 $\log_{10}$ cfu/gram) have we any evidence for potential detection of contaminated food (see Footnote 90)."

It would be possible to add what-if scenarios for hot-holding, but they do not advance the primary aims of the risk assessment, since the number of predicted hot-holding illnesses are essentially independent of the growth during stabilization (with our assumption that heating prior to hot holding is sufficient to kill all vegetative cells).

190. Comment:

Criteria 2: Identification of data and critical evaluation of evidence.

The report provides a well-structured presentation of information regarding hazard identification in Chapter 2, including information on effects, incidence, epidemiology, summary information of specific outbreaks, and clinical presentation of C. perfringens Type A food poisoning. The evidence presented regarding hazard identification establishes that C. perfringens poses a hazard and provides the key characteristics of the hazard, including steps in pathogenesis, especially susceptible subpopulations, and especially important scenarios of exposure (e.g., temperature abuse in institutional and restaurant settings) that are of importance to structuring the risk assessment. The main hazard is diarrheal illness, but this illness can combine with other complications to cause more severe effects, especially for elderly.

190. Response:

No response is necessary.

191. Comment:

Table 3.1 provides a rationale for the identification and selection of food categories that are included in the risk assessment. The categories are based upon time-temperature histories expected. Thus, foods are grouped into a category if they will have similar heating and hot-hold patterns, even though the foods may be different in terms of whether it is beef, chicken, or other examples. This categorization seems reasonable from a modeling perspective.

191. Response:

No response is necessary.

192. Comment:

From the CFSII database, information is obtained regarding the mass of the serving, meat constituent fraction of the serving, and fraction of the serving that is a particular type of spice. The salt content is also obtained and is used to modify growth rate estimates.

192. Response:

No response is necessary.

193. Comment:

The authors do a good job of explaining why some studies were excluded and others included as a basis for input information to the risk assessment. There is extensive citation of literature and databases. The authors are very consistent in clearly identifying which studies were considered for a particular model input, why some studies were excluded and why others were included as a basis for quantifying inputs to the model, and how the quantification was done.

193. Response:

No response is necessary.

194. Comment:

Criteria 3: Overreaching logical structure of the risk assessment.

The risk assessment follows accepted practice in terms of overall structure. The major risk assessment steps of hazard identification, exposure assessment, hazard characterization, and risk characterization are made clear by the structure of the document. Each of these four major steps has a dedicated chapter.

194. Response:

No response is necessary.

195. Comment:

Key factors considered in the risk assessment include types of RTE and partially cooked foods eaten, serving size, frequency with which they are eaten, and the number of C. perfringens cells in each serving. There is variation in the characteristics of each serving, including how they are treated. There is also uncertainty because of lack of knowledge. Variability and uncertainty are quantified using Monte Carlo simulation.

195. Response:

No response is necessary.

196. Comment:

Variability is quantified using probability distributions. For example, the concentration of C. perfringens spores in raw meat varies from time to time and from place to place. Each serving of RTE or partially cooked food differs in size and composition.

196. Response:

No response is necessary.

197. Comment:

The text on page 28 is not entirely clear as to how uncertainty is separately characterized compared to variability. The text here seems to be written for a general audience, but as a result suffers from lack of clarity and could benefit from clearer use of technical terms. For example, the authors often use the term "parameter", which is confusing because this term is used both to refer to inputs to a model as well as parameters of a model (the latter are constants that are typically selected based upon some type of calibration process). For example, a gamma distribution for variability has two parameters, which can be estimated by fitting a distribution to data. In contrast, quantities such as the size of a serving, are inputs to the model, not parameters. The authors are strongly encouraged to consider the use of terms "input" and "parameter" as referring to two different types of quantities. A glossary of some terms might also be helpful.

197. Response:

We agree that the issue of nomenclature is confusing, and the review draft attempted brevity with a lack of specificity; the result at the cited location was, as the reviewer notes, undoubtedly confusing. However, the problem is a little more difficult here than implied by the reviewer because of the presence of both variability and uncertainty, and the lack of standard nomenclature. Thus the parameters of the variability models are not constants, but are random varieties derived from the uncertainty distributions; only the parameters of the uncertainty distributions are constants, hence parameters in the sense given here by the reviewer. The reviewer's recommendation on the definition of parameters is thus incomplete. The size of a serving is indeed an "input" in one sense, in that the variability distribution used here is the empirical distribution; but that is not

fundamental. We have re-written the offending section of Section 3.1 to clarify these issues.

A glossary is useful if terms have accepted definitions across all fields. We have not attempted such a glossary in this risk assessment, because we found substantial cross-specialty mixing of definitions — terms mean different things to different specialists. Where possible, we have used such terms with the appropriate meaning in the appropriate places in the assessment.

198. Comment:

The use of the term "guesswork" on page 28 is somewhat questionable. Perhaps it was truly "guesswork" or perhaps the authors are intending to be extremely frank about the lack of pedigree of some of the available information. On the other hand, if there was a process of expert judgment, rather than just guesswork, it would be better to describe this process and to describe it as being based upon expert judgment (if applicable).

198. Response:

We truly meant "guesswork." There are values, such as the fraction of the selected foods that are RTE or partially cooked, and the fraction of Category 1 and 4 foods that are hot held, on which we have essentially zero information, and for which we could identify no useful surrogates (in the sense of having more information available for those surrogates). The values used were not obtained by expert judgment or any formal process; they are literally guesses.

199. Comment:

Aside from the "big picture" steps of risk assessment, the authors also describe four key steps that pertain to the exposure assessment. These steps include: (1) processing of food (pre-retail); (2) transportation and storage; (3) preparation (e.g., reheating); and (4) hot holding. This structure is consistent with information presented in the hazard identification chapter, which implies that "temperature abuse" is a key concern. Thus, the model structure enables evaluation of a variety of temperature history patterns.

199. Response:

No response is necessary

200. Comment:

Criteria 6a: Appropriateness of modeling techniques

The mathematical equations presented in the exposure assessment chapter, such as Equations 3.1, 3.2, and 3.3, appear to be appropriate. The use of integer numbers for the number of cells is appropriate. The assumption that growth or death processes are not constrained by integer values does not seem like a significant limitation of the model, and no doubt simplifies the model formulation. As the authors appropriately point out in footnote 5 on page 32, the rounding to the

next lowest integer value will have little effect on the accuracy of results if the number of cells is reasonably large (e.g., more than a few thousand). As noted in the hazard identification chapter, a substantial number of cells are required to cause an adverse effect. Therefore, this limitation is quite reasonable.

200. Response:

The initial number of vegetative cells and spores in servings that are predicted to cause illness is often very low (it is common for a single initial vegetative cell to be predicted to cause illness). The discussion of Section 3.11.4 was previously incorrect in suggesting that most illnesses arise from servings with cell densities of order 100 CFU/g, and this has been corrected. The variability between servings may thus be underestimated by the approaches taken in the risk assessment, particularly in assuming the same fixed growth during stabilization for all servings is possible. However, no alternative method of analysis currently exists — a full analysis would require replacing the deterministic growth equations with a probabilistic approach, and no experimental data are currently adequate to support the development of such an approach. We have added an additional assumption in Section 4 to indicate the existence of this potential problem, namely "The variability incorporated in the growth modeling is adequate to represent the stochastic processes that probably occur at low cell densities (particularly the likely stochastic variation in delay times)."

201. Comment:

Footnote 6 on page 33 refers to the numerical precision of the simulation. Suggest that the term "numerical precision" be used instead of "numerical uncertainty," although the point made is of course correct.

201. Response:

We have adopted the suggested nomenclature.

202. Comment:

A number of inputs are assigned distributions based upon expert judgment, rather than data analysis. For these inputs, it appears that the distributions are intended to represent variability (e.g., fraction of spores that germinate in favorable conditions). The lack of knowledge associated with specifications of these distributions are dealt with in sensitivity analysis. However, in principle, uncertainty regarding end points and modes of triangular distributions could be incorporated into the uncertainty dimension of a two-dimensional Monte Carlo simulation.

202. Response:

Indeed, that would be true, except that we have no idea about the size of the uncertainty. The "expert judgment" in these cases is limited to either evaluation of the very few studies that are available, or pure guesswork. Attempting to

invent uncertainty distributions would strain credulity, and we believe would not improve the analysis.

203. Comment:

As the authors note on page 71, further testing of the effect of the variance parameter *a* might be appropriate.

203. Response:

This would be possible, but is extremely labor intensive (it essentially requires the complete re-analysis of the growth experiments, although the spreadsheets are set up to do that). It would also not have a significant effect on the risk assessment, since the only part of the assessment that is directly affected is in the evaluation of growth from spores during hot-holding. The number of illnesses caused by such growth is independent of the growth during stabilization, so is of secondary interest to the risk assessment; and the uncertainty in the number of such illnesses is already extremely high because of our lack of knowledge of the fraction of servings that are hot held and because of the possibility for cross contamination during hot-holding.

For the main part of the assessment, only the growth rates during the exponential growth phase are used; and these are (or should be) practically independent of the estimated value of *a*.

204. Comment:

There is a complex presentation of the methods used to model growth rates, but there is not sufficient information presented (e.g., in Section 3.10.3) for the reader to evaluate the goodness-of-fit or agreement of the model with the data used to calibrate the model. A graphical comparison of the model with the data, for example, would have been helpful. The comparison of the model to other studies is useful, and the basis for the bias correction multiplier of 1.739 appears to be reasonable.

204. Response:

There are so many growth data that presentation of fits would take a huge amount of space, and provide little useful information. Examples of comparison between primary model fits and data are presented in the accompanying spreadsheet (CP_fixed_temp.xls), and all the data and predicted values are given there (allowing the interested reader to construct more graphics). Similar fits to mathematical functions with similar shapes as the primary model used here are shown in several of the original papers, and there is little to choose between primary model functional forms. In the literature generally, formal goodness-of-fit estimates to such primary models are unusual, because the fits are usually obviously within the range of variability of the experimental systems used; large deviations are usually explained or explicable by observed upsets in the experimental systems.

205. Comment:

In general, the modeling techniques appear to be reasonable, and are based upon citations to literature (e.g., with respect to issues such as growth rates).

205. Response:

No response is necessary.

206. Comment:

Page 91 – the authors should comment on the extent to which negative estimates for standard deviations of the lognormal distribution were realized. If this occurs infrequently, then this is approach is probably okay. If substantial truncation was required, then this is approach may not be the best choice.

206. Response:

The footnote describing the occurrence has been modified to say "This occurs less than 0.001% of the time for temperatures above 0 °C and less than 4% of the time for temperatures below 0 °C, and in such cases the standard deviation is set to zero. This approximation was considered adequate, because the uncertainty in death rates during cold storage contributes so little to the overall uncertainty."

207. Comment:

The approach for intra-household serving to serving variability is based upon some assumptions. The sensitivity of the results to these assumptions should be evaluated.

207. Response:

The reviewer is correct, but the primary assumptions are of a form that cannot be adequately evaluated using sensitivity analysis, since they are representativeness assumptions (and we have no alternatives to evaluate in any sensitivity analysis). This is acknowledged in Section 4 (Limitations of the Exposure Model).

208. Comment:

Minor comment: "D-value" should be defined in Table 3.31 for convenience of the reader.

208. Response:

A summary definition has been added as part of footnote b.

209. Comment:

The authors might comment on the consistency of input information for this risk analysis. In some cases, what appear to be somewhat crude judgments are made with regard to triangular distributions, while in other cases very complex calculations are performed to arrive at distributions or parameter values for specific models.

209. Response:

See Response 43.

210. Comment:

For cases in which the authors state that the uncertainty of a distribution was considered small enough to ignore, it is preferred if the authors give a quantitative criterion for a threshold of uncertainty below which the uncertainty can be ignored, and some justification for this assumption (e.g., by comparison with more important sources of uncertainty in the assessment).

210. Response:

It is difficult to respond to the reviewer's comment without a specific example. Where meta-analyses of experimental data were performed, uncertainties were always included. Where empirical data were used as inputs, they were considered representative, so the only uncertainty is incorporated in the representativeness assumption. In two cases (Figure 3-15, and Figure 3-17), fitted distributions were used in place of the empirical distributions that were considered representative, and the resulting uncertainties are so obviously trivial that no formal analysis was performed. For quantities that had to be evaluated by sensitivity analysis, no uncertainties can be assigned, as discussed in the text.

211. Comment:

Values that are treated as assumed constants, e.g., fraction of servings that are hot-held, are good candidates for sensitivity analysis.

211. Response:

That is correct, so such values are indeed treated by sensitivity analysis, see Section 6.6 in general, and Section 6.6.11 in particular for the fraction of servings of Category 1 and 4 that are hot-held.

212. Comment:

The appendices of Chapter 3 are very useful. However, these could be placed as appendices at the end of the report to have better flow of information in the main body of the report.

212. Response:

We have maintained the current layout, not through any great preference but because the effort involved in changing the layout exceed the utility of it.

213. Comment:

In comparison to the complexity of the model, the results that answer the risk management questions appear to be relatively simple. The authors might provide some context to the reader, perhaps in a summary at the end of each chapter, or in Chapter 6, as to the parts of the model that are really the most critical, and regarding parts of the model that turn out to be unimportant. As the reader goes through Chapter 3, for example, there is perhaps a presumption that each equation is equally important. When building a model, it is often tempting to do the best job possible on each component, even though some components may matter little to the final answer. Conversely, however, some components may be of such critical importance that additional resources should be devoted to their formulation. Some clear messages long these lines regarding priorities for model refinement would be useful.

213. Response:

The reviewer is completely correct with respect to the overall results; and indeed, while building the model we did attempt "to do the best job possible on each component, even though some components may matter little to the final answer," primarily because we did not know at the time which parts might turn out to be important, and because it is always very difficult to not do the best job possible once one gets started on doing any sort of job.

We have provided some indication of where additional resources need to be devoted in Section 7, but the main need is for additional data, not for additional effort on model formulation.

We give some guidance as to the most important parts of the model for the overall results in the new Section 6.1.2 (see also Response 70). However, we caution against going too far in this respect. For example, we provide breakdowns of results by various sources in Section 6.3, and some of the breakdowns show very small component contributions; however, such contributions may be important for some reason to FSIS, so we are loathe to prioritize modeling resources too strongly without knowing exactly what components may subsequently be of interest.

214. Comment:

Criteria 6b: Methodologies Used for Estimating Parameters from the Data

An example of parameter estimation is described on pages 44-45, in the case of the concentration of C. perfringens in cooked meat in RTE foods. In this case, the scale parameter was set equal for distributions fit to data of each of three different studies. However, the shape parameter was allowed to differ in two cases – one parameter value was estimated based upon a combination of

two studies, and another parameter value was estimated based upon a third study. The rationale for the two values for the shape parameter is to support uncertainty analysis.

214. Response:

The reviewer is not quite correct as to the rationale. The actual rationale for different distributional parameters was because the two distributions were expected to be different, since one was for a larger group of organisms than the other. It then turned out that the scale parameters of the distributions tested as equal. This happenstance was convenient, in that it allowed relatively easy enforcement of the required inequality in the uncertainty analysis by enforcing an inequality in the two shape parameters; but it is incorrect to say that the rationale for choosing two values is to support the uncertainty analysis.

215. Comment:

Uncertainties in the parameters of the gamma distribution were estimated using likelihood estimation and transformations in order to obtain normal error structures. The maximum bound of the shape parameter estimated from the third study was used as a constraint on the uncertainty distribution for the shape parameter. It appears to be the case that the upper bound for the shape parameter, a_T, also has an uncertainty distribution. This would be appropriate, since the knowledge of a_T is limited by the finite data set from which the estimate is made.

215. Response:

As now explained in the new Section 3.3, the transformations were not so much to obtain a normal error structure as to obtain an approximation to the likelihood function that could be rapidly sampled and that included the main features of the likelihood function, including the correlation structure particularly near the maximum likelihood.

216. Comment:

While the transformation to obtain normal error structures is plausible, a concern nonetheless is whether a back-transformation properly preserves the dependence between distribution parameters. The authors should provide a graphical comparison of the probability bands for the distribution of variability versus the original data in order to confirm that the simulation adequately captures the characteristics of the data while also providing a plausible estimate of variability.

216. Response:

As explained above, and in the new Section 3.3, the transformations were chosen not so much to obtain normal error structure, but to obtain approximations to the likelihood function that could be rapidly sampled and that preserved the main features of the likelihood structure, including the correlations structure, near the maximum likelihood. The transformations were obtained in such a fashion that the profile likelihoods for the individual parameters were very close to normal

(usually the correlation coefficient between the square root of the logarithm of profile likelihood deviation from the maximum likelihood and the transformed parameter value was larger than 0.998), so probability bands for marginal distributions should be as accurate as is possible with likelihood approximations. The correlation structure was then approximated by approximating the structure of the likelihood function in the transformed variables by a multinormal distribution. This approximation was performed by numerically approximating the information matrix, with the numerical step sizes for derivative estimation chosen to be approximately equal to the standard deviations of the marginal distributions. This ensured that correlations out to around 1 standard deviation of the marginals were reasonably accurately incorporated.

To examine the adequacy of the approximations, we examined 2-dimensional arrays of differences between the normal approximations and the likelihood deviation from the maximum likelihood, and found that the differences between these surfaces generally were less than a few percent, although we have not attempted to convert the deviations into differences in approximate probability intervals.

The reviewer calls for graphical displays of these differences (which would require, at minimum, 3-D plots of approximations to probability bands) to be included in the text, but we believe that such relatively obscure technical data are not appropriate in this text. In addition, the approach adopted was not designed in any attempt to obtain highly accurate fiduciary intervals, but to incorporate with reasonable accuracy the major structure of the likelihood function.

217. Comment:

Since a similar methodology is employed for other inputs (e.g., C. perfringens vegetative cell concentrations in partially cooked food), the same comments apply.

217. Response:

See Response 216.

218. Comment:

An alternative to the use of likelihood estimation with transformations is to employ bootstrap simulation as a method for estimating sampling distributions for the distribution parameters, as well as the dependencies between the sampling distributions. For example, Frey and Rhodes (1998) illustrate example results for gamma distributions that demonstrate the complex inverse and nonlinear dependence between the uncertainties of the distribution parameters. As noted in that example, a correlation coefficient is not an adequate measure of dependence. In this risk assessment, the implications of the back-transformation with respect to proper characterization of dependence between the distribution parameters should be tested and visualized.

218. Response:

We considered using bootstrap analyses, but rejected it as being too computationally intensive in this situation. The structure of the data is sufficiently complex that bootstrap analysis would require highly individualized analysis methods for almost every experiment examined, each requiring specialized code to be written for parameter estimation.

Frey and Rhodes (Frey, H.C., and Rhodes, D.S. 1998. Characterization and simulation of uncertain frequency distributions: effects of distribution choice, variability, uncertainty, and parameter dependence. *Human and Ecological Risk Assessment* 4:423–468) examined a parametric bootstrap for the gamma distribution and showed the expected inverse and non-linear dependence in the joint distribution of parameter values. This inverse non-linear dependence is expected since in the parametric bootstrap all sample sets (from which estimates of parameters are made) come from the originally estimated gamma. The shape and scale parameter estimates a and b can thus be expected to satisfy $ab \sim$ constant, since that product is just the mean of the estimated distribution, which will approximate the mean of the originally estimated gamma. In such circumstances it is often possible to obtain better approximation to correlation structures by re-parameterizing (in this case, for example, to a and ab) to remove such trivial correlations.

We examined this possibility in several cases, and chose parameterizations accordingly. For the gamma distribution, re-parameterization in terms of $\ln(a)$ and $\ln(b)$ reduces the major non-linear, inverse, correlation to a trivial linear correlation. As we mention in Response 216, we have examined the approximation between likelihood function and its approximation; but we consider such comparisons to be too highly technical to be included in the text.

219. Comment:

In general, the authors should either report the results of goodness-of-fit tests, provide visual comparisons of the fitted distributions and the observed data to which the distributions were fit, or some combination of the two. This would also serve as a quality assurance check that the fitted distribution is in fact an appropriate representation of the data.

219. Response:

Where goodness-of-fit tests were possible, we have reported them. For many of the data, however, standard goodness-of-fit tests (such as distributional or chi-square tests) cannot be used because of the extreme sparseness of the data (*e.g.* the *C. perfringens* concentration data). Developing goodness-of-fit tests in such cases would have been a major enterprise in itself, and not fruitful in that they would necessarily not be powerful. We note that the reviewer does not provide any example where we have omitted a goodness-of-fit test that the reviewer thinks could be supplied. Similarly, where possible we have graphically shown the comparison between the data and the fit. In other cases, no such graphical comparison is possible because of the nature of the reported data — again, the *C.*

perfringens concentration data are a good example, where we have very few reported data each consisting of numbers of samples with given numbers of observed cells, or a more complex set of reported data with multiple possible interpretations (see Table 3.4 for example).

220. Comment:

Similar to the last comment for the preceding criterion, one can potentially get lost in the details of parameter estimation and lose the context as to which inputs matter the most and which are relatively unimportant. The authors might give the reader some hints along these lines by indicating which parameter estimates are later shown to be critically important and which are later shown to be relatively unimportant.

220. Response:

See Response 213.

221. Comment:

Critera 7: Have the risks been appropriately characterized.

Chapter 7 focuses on risk characterization. There are few data with which to compare model predictions of risk characterization. The authors compare model results with an estimate reported by Mead et al. (1999) and argue reasonably convincingly that the model estimate is in reasonable agreement.

221. Response:

No response is necessary. (A typographic error; it is Chapter 6 that focuses on Risk Characterization.)

222. Comment:

The numerical precision of the Monte Carlo simulation is shown to be adequate for purposes of estimating illnesses per million servings for different growth rates during stabilization.

222. Response:

No response is necessary.

223. Comment:

A comparison of Figures 6-2 and 6-1 reveal that the range of uncertainty inherent in any estimate of illnesses per million servings is greater than the variability in the median estimate of this quantity among the different growth levels considered. This implies that uncertainty is large relative to variability in the risk characterization.

223. Response:

This is not quite correct. Figures 6-2 and 6-1 show the uncertainty, but the variability (between servings) has been averaged out. The variation with growth during stabilization is not variability in the sense used in the risk assessment, since the growth during stabilization is common to all servings. While the uncertainty is larger than the variation with growth during stabilization, we can still draw conclusions about how the number of illnesses varies with growth during stabilization; but our absolute knowledge of the number of illnesses is very uncertain.

224. Comment:

Section 6.3 is critically important because this is a form of sensitivity analysis to help identify the key sources of variability in the assessment. This analysis provides useful insight into the roles of meats versus spices, and regarding the contributions of each food category.

224. Response:

No response is necessary.

225. Comment:

Criteria 8a: Identification and characterization of key sources of variability and uncertainty

Section 6.3 provides insight regarding key sources of variability in the assessment, at least in terms of the proportional contribution of different factors to the total risk estimates.

225. Response:

No response is necessary.

226. Comment:

Section 6.6 reports on a sensitivity analysis that appears to be focused on inputs that were assigned point estimates or probability distributions based on judgment (e.g., uniform or triangular distributions). The authors appear to use a local sensitivity method, in which each input is perturbed individually while others are left unchanged. However, it could be the case that other inputs for which distributions were assigned were allowed to vary according to their distributions. This could be made more clear in the text. It is not very clear as to how the sensitivity was actually measured, in terms of the categories "t, n, and a" mentioned in the last column of Table 6.6. Although the text on page 152 implies that the methodology is further discussed on the following pages, it was not very clear as to how a quantitative sensitivity measure was obtained in all cases. Also, in some cases, it was not simply a perturbation of an input with respect to a central value, but rather a change in the distribution of the input that was

assumed (e.g., heating time in a microwave oven). It is not clear how this fits into the framework of Equation 6.4.

226. Response:

See also Response 234. We did indeed perform a local sensitivity analysis as suggested by the reviewer. The details of the sensitivity analysis were very abbreviated, and have been considerably extended in each sub-section of Section 6.6 to detail exactly how the results of Table 6.6 were obtained in each case. It has been made clear that each such sensitivity analysis requires a complete Monte Carlo run to obtain the change in estimated number of illnesses per year. In cases where a whole distribution was changed, there are two possibilities. In the first case, it was demonstrated that the result depends primarily on a particular statistic of the distribution (*e.g.* the mean), and the sensitivity analysis was performed on that statistic. Second, for cases where the sensitivity is small (*e.g.* heating time in a microwave oven), only a gross measure (in this case the mean heating time) was used as the sensitivity parameter.

227. Comment:

Section 6.6 should have a summary of the most sensitive inputs, based not only on the results of Table 6.6 but on authors' judgment as to the relative ranges of the inputs. There could be a stronger link between the results of Section 6.6 and some of the recommendations in Chapter 7.

227. Response:

See Response 213.

228. Comment:

It would have been useful if the authors could have performed a sensitivity analysis based upon the Monte Carlo simulation results in order to identify key sources of variability and key sources of uncertainty, using techniques such as correlation coefficients, regression analysis, or analysis of variance (ANOVA). Although there is an analysis in the risk characterization section that apportions the risk to specific causes, it would be helpful to have some idea as to which sources of variability are more important than others. For example, where is it worth spending the next dollar to get more data to better characterize variability in a model input?

228. Response:

There is no "key" source of variability; variability is the natural variation that is present, in this case between servings. The final results that we examine have no variability, since it is averaged out in the final measures of interest (the numbers of illnesses) — the variability contributes to the numerical imprecision only, which we make negligibly small by using sufficient samples. Were we interested in other final measures that involved variability, such an analysis might be of interest.

However, it would be possible to use the techniques identified by the reviewer to identify the relative contributions of various sources of uncertainty, and to perform an evaluation of the cost-effectiveness of obtaining better data to reduce uncertainties (this is practically the same thing as better characterizing variability). The program is not currently set up to evaluate uncertainty correlations of the nature discussed, but we will investigate the implementation of such an analysis. At the moment, it is not clear whether the measures obtained would, in fact, be of substantial assistance, because the major uncertainties are those that have not been quantified and that are related either to representativeness of the data or to completely lack of knowledge about certain parameters.

229. Comment:

With regard to uncertainty, given that the range of uncertainty for a given growth level is larger than the variation in number of illnesses per million servings when comparing growth levels, there could be a clear, quantitative ranking as to which quantified uncertainties in the model are contributing most to uncertainty in the risk characterization. This information could help support the recommendations in Chapter 7. Of course, the authors would appropriately want to incorporate unmodeled issues or other qualitative sources of uncertainty into the discussion.

229. Response:

The reviewer is, we think, somewhat confused over the interaction between uncertainty, variability, and the growth during stabilization (see also Response 223). While the uncertainty in numbers of illnesses is large compared with the variation that occurs in the number of illnesses as the growth during stabilization increases, that uncertainty does not obscure in any way the variation of number of illnesses with growth. To get this point across, we have tried to improve the discussion following Equation 6.1 by adding the sentence, "The corresponding equation then shows the variation with growth at this percentile of the uncertainty distribution" at the end of Section 6.2.2. As the reviewer recognizes, the relative rankings of the recommendations in Chapter 7 are based not only on the relative contribution to uncertainties, but also on some idea about the relative difficulty and cost of obtaining the required information.

230. Comment:

As noted in some previous comments, in addition to prioritizing key sources of variability and uncertainty in model inputs and parameters, it is useful to prioritize the importance of different parts of the model.

230. Response:

See Response 213.

231. Comment:

Criteria 8b: Identification and characterization of critical assumptions

No external contamination with C. perfringens is assumed, as stated on page 33.
The properties of spores are assumed to be independent of the spice (page 36).
Because of lack of data, there is lack of stratification with respect to factors such as distinction between beef, chicken, and pork, and between whole muscle vs. ground meat, or cured vs. uncured products. The authors point out that this tends to underestimate the total uncertainty and could lead to inaccurate estimates of exposure.

231. Response:

All the assumptions listed here are now (see Response 232) included in Section 4, and all of these particular assumptions come under the heading of representativeness assumptions.

232. Comment:

In general, it is suggested that the authors do a search through the document for words such as "assume" or "assumption" and be sure that each such example given in the main body anywhere in the report is also listed in Chapter 4. For example, on page 57 "assume that C. perfringens in spices are present entirely as spores" but does not seem to be in Chapter 4. Rather than enumerate all such cases here, it would be easy for the authors to do the search through the document as suggested here. In general, the authors do an excellent job of identifying assumptions throughout the document, and it will be helpful to have all of them collated into Chapter 4. The authors may wish to create additional subcategories in Chapter 4 to make it easier for the reader to review the key assumptions.

Chapter 4 precedes the hazard and risk characterization chapters, which involve additional assumptions. Perhaps Chapter 4 could be moved to later in the document, and incorporate all key assumptions from all components of the assessment.

232. Response:

Such a search is an excellent idea, and one that we have followed. Not all assumptions are listed explicitly, since some are best treated generically (*e.g.* assumptions about normality of error distributions in various analyses), but we believe that all assumptions are now included at least generically in the list. Specific assumptions about the values of inputs that are examined in the sensitivity analysis have been excluded. We have also followed the reviewer's suggestion and expanded the subcategories of assumptions.

We have not, however, mixed the listing of assumptions in the exposure and hazard characterization sections. It is standard in risk assessments such as this to keep these two sections separate, so we have maintained that separation even in the assumption lists.

233. Comment:

The listing of key assumptions in Chapter 4 should be in some kind of priority order. Ideally, the priorities should be based upon quantitative sensitivity analysis for those inputs for which variability and uncertainty were quantified and for which assumptions were embedded in the estimates of variability and uncertainty. For inputs, parameters, or model structures that involved more highly qualitative judgments, or for unmodeled issues that may be of substantial importance, judgment should be used to provide a priority listing. For example, it would be helpful to categorize assumptions as being of major importance, moderate importance, and minor importance.

233. Response:

We agree that it would be desirable to place these assumptions in priority order, but decline the attempt. We believe that we would be sufficiently wrong sufficiently often that such an attempt would be more likely to mislead than to enlighten. It was only by examining the results of the modeling that certain "obvious" properties of the inputs about which we have substantial information became apparent in hindsight (for example, that most of the predicted illnesses arise because, essentially, of broken refrigerators). We are practically certain that the same lack of foresight would apply to our list of assumptions; the more so because of our substantial lack of knowledge that required the assumptions in the first place.

234. Comment:

Criteria 10: Clarity of the risk assessment report

In general, this report was well written and appears to be comprehensive. The assessment objectives are clearly stated and analyses are presented based upon the objectives. The limitations of input information are carefully described and key assumptions are conveniently listed in Chapter 4. The interpretation of data appears to be reasonable. The modeling methodologies appear to be acceptable, although there could be alternative approaches. One area in which the work could perhaps be improved is with regard to the sensitivity analysis. It appears that the authors performed essentially a local sensitivity analysis using a method that is appropriate for linear models, but that may not be reliable when applied to nonlinear models. The method appears to be a variant of differential sensitivity analysis. Furthermore, the effects of possible interactions among inputs is not addressed. A statistical method such as ANOVA would be more robust and might reveal insights regarding not only the main effects of individual inputs, but also interaction effects of various kinds.

234. Response:

We agree that the sensitivity analyses could be extended in the way suggested; however, extensions could be made in most areas of the analysis, and the question arises as to whether such extensions would be useful for the primary purpose of the assessment. The sensitivity analyses were performed in order to gain some insight into which are the most important of the inputs about which there is very

little information; and the differential approach applied does precisely that. It is true that there may be interactions between inputs (indeed, for most of the inputs we expect approximately multiplicative effects on the number of diarrheas, because of the structure of the model). However, quantitative or even qualitative estimates of such interactions are of no additional value at this point *for the primary purposes of this risk assessment*. That is not to say that further work should not be done to clarify any such effects; but there is no need in this document (which is already sufficiently long and complex).