Part 5.

Risk characterization: response to Codex questions

5.1 INTRODUCTION

This section addresses the three risk questions posed by CCFH in 2001 in relation to the risk from *L. monocytogenes* in RTE foods. The specific question addressed is given in each case.

5.2 QUESTION 1

Estimate the risk from L. monocytogenes *in food when the number of organisms range from absence in 25 grams to 1000 colony forming units per gram, or millilitre or does not exceed specified levels at the point of consumption.*

The question posed by the CCFH primarily requires a consideration of how the relative risk of acquiring listeriosis is affected by the level of *L. monocytogenes* present in a serving of food at the time of consumption. The ability to answer this question is dependent on the ability to articulate and interpret dose-response relationships for *L. monocytogenes*. However, there are a number of potentially confounding factors that could influence the approach taken and the complexity of the answer provided. In view of the generic nature of the CCFH question and the fact that this is one of the first microbial risk assessments requested by CCFH, it was decided that the response to this question should focus on communicating the key risk assessment concepts. It is also important to note that this question implies a series of comparisons based on relative risks and does not require the much more daunting task of calculating absolute risk. Accordingly, consideration of potential confounding factors was limited and a detailed consideration of uncertainty and variability was not undertaken in addressing this question. An introduction to issues related to the uncertainty and variability associated with dose-response models is provided in the hazard characterization section of this document. In addition to not explicitly addressing uncertainty and variability, a number of simplifying assumptions were made in developing the examples used to answer the question posed by CCFH. For instance, to calculate the ingested dose, knowledge of the size of the serving is needed. A fixed serving size of 31.6 g was assumed for convenience to simplify the calculations because it approximates a typical serving size and because dose levels were estimated in 0.5 $\log_{10}$ increments ($10^{0.5} = 3.16$). To calculate the concentrations for other serving sizes in the tables that follow, the dose levels would have to be divided by the serving size.

As discussed in the hazard characterization, the exponential model was selected to describe the relationship between the dose of *L. monocytogenes* ingested and the probability of developing systemic listeriosis. Dose-response curves were developed for both the healthy

population and the susceptible population and include the entire range of ingested doses (i.e. not restricted to 1000 CFU/g food). These curves are population based and describe the average dose-response relationship. A specific outbreak that involves a strain with high virulence or an unusually susceptible population may still result in a significant number of cases from food containing comparatively low numbers of *L. monocytogenes*. For the purposes of this example, only the dose-response curve for the susceptible population was used, and it was assumed that all cases of listeriosis were restricted to that population. The specific dose-response curve selected was the one where the maximum level to which *L. monocytogenes* could grow in a food was assumed to be $10^{7.5}$ CFU/serving. The end result of these assumptions is that the most "conservative" dose-response model was used, i.e. the maximum virulence of *L. monocytogenes* was assumed. The r-value for this relationship was 5.85×10^{-12} (Table 2.18). The dose ingested is a function of the level of the microorganism in the food (CFU/g) multiplied by the size of the serving. Thus, the equation for calculating the probability of listeriosis was:

$$P = 1 - e^{(5.85 \times 10^{-12})(31.6g \times n)}$$

where *n* is the number of *L. monocytogenes* per gram. By substituting different values for *n*, the likelihood of listeriosis at levels between 0.04 (1 CFU/25 g) and 1000 CFU/g was calculated.

The overall affect on the number of cases of listeriosis was estimated by multiplying the likelihood of listeriosis per serving by the total number of servings. For this calculation, the total number of RTE servings was assumed to be 6.41×10^{10} servings, i.e. the estimated total number of servings per year consumed in the United States of America for the 20 classes of RTE food considered in FDA/FSIS (2001). The corresponding number of listeriosis cases for the susceptible population was considered to be 2130 (FDA/FSIS, 2001), and will be used to represent the current incidence of listeriosis when comparing the effect of changes to incidence under different theoretical scenarios.

As a simple, worst-case scenario, the predicted risk per serving and predicted number of annual listeriosis cases were estimated by assuming that all 6.41×10^{10} servings had the maximum contamination level being considered. The effects on the incidence of listeriosis of six levels of pathogen were evaluated (0.04, 0.1, 1, 10, 100 and 1000 CFU/g) (Table 5.1).

A more realistic approach would be to use a distribution of *L. monocytogenes* levels in foods when consumed. To explore that more complex approach, the overall distribution of *L. monocytogenes* levels in 20 classes of RTE foods from the FDA/FSIS (2001) risk assessment was used (see Table 5.2) to calculate the probability of listeriosis and the predicted number of cases. At each maximum *L. monocytogenes* level considered, the number of servings from the distribution exceeding the designated contamination level was added to that maximum level. For example, for an upper limit of 1000 CFU/g, the number was 1.18×10^8 servings, i.e. 6.23×10^7 (servings originally predicted to be at 1000 CFU/g) + 2.94×10^7 (servings originally predicted to be at 10 000 CFU/g) + 1.39×10^7 (servings originally predicted to be at 10^5 CFU/g) + 3.88×10^6 (servings originally predicted to be at $10^{5.5}$ CFU/g) + 8.55×10^6 (servings originally predicted to be at $>10^6$ CFU/g). The predicted annual numbers of listeriosis cases were calculated and summed, and the predicted number of cases for each maximum level is given in Table 5.3.

Table 5.1 Probability of illness per serving for the susceptible population estimated for different levels of *Listeria monocytogenes* at the time of consumption and the estimated number of cases per year in the United States of America if all RTE meals were contaminated at that level.

Level (CFU/g)	Dose[(1)] (CFU)	Log_{10} dose (log_{10} CFU/ serving)	Probability of illness per serving	Relative risk[(2)]	Estimated annual number of cases[(3)]
<0.04	1	0	7.39×10^{-12}	1	0.54
0.1	3	0.5	1.85×10^{-11}	2.5	1
1	32	1.5	1.85×10^{-10}	25	12
10	316	2.5	1.85×10^{-9}	250	118
100	3 160	3.5	1.85×10^{-8}	2500	1 185
1000	31 600	4.5	1.85×10^{-7}	25000	11 850

NOTES: (1) Serving size of 31.6 g. (2) Using the risk from a dose of 1 CFU as reference. (3) A total of 6.41×10^{10} servings per year assumed.

Table 5.2 Predicted distribution of levels of *Listeria monocytogenes* occurring in RTE foods.

Level of *L. monocytogenes* in a food at consumption (CFU/g)	Number of servings at the specified dose
<0.04	6.18×10^{10}
0.1	1.22×10^{9}
1	5.84×10^{8}
10	2.78×10^{8}
100	1.32×10^{8}
1000	6.23×10^{7}
10000	2.94×10^{7}
100000	1.39×10^{7}
316000	3.88×10^{6}
>1000000	8.55×10^{6}
Total	6.41×10^{10}

SOURCE: FDA/FSIS, 2001.

Table 5.3 Predicted annual number of listeriosis cases in the susceptible population when the level of *Listeria monocytogenes* was assumed not to exceed a specified maximum value and the levels of *L. monocytogenes* in the food are distributed as indicated in Table 5.2.

Level (CFU/g)	Maximum Dose[(1)] (CFU)	Percentage of servings when maximum level[(2)]	Estimated number of listeriosis cases per year[(3)]
0.04	1	100	0.5
0.1	3	3.6	0.5
1	32	1.7	0.7
10	316	0.8	1.6
100	3160	0.4	5.7
1000	31 600	0.2	25.4

NOTES: (1) Serving size of 31.6 g. (2) Number of servings in the highest *L. monocytogenes* level assumed divided by 6.41×10^{10} times 100. (3) Levels of *L. monocytogenes* per serving used to calculate predicted number of cases based on the overall distribution from the FDA/FSIS risk assessment (2001) (see Table 5.2). A total of 6.41×10^{10} servings per year was assumed.

Tables 5.1 and 5.3 show vast differences in the estimated number of cases for the worst-case answer to the question (Table 5.1) compared with that estimated when an attempt is made to consider the frequency and extent of contamination actually encountered in RTE foods (Table 5.3). While either set of predictions can be challenged on the basis of the assumptions used, such scenarios are useful in framing the extent of the risk likely to be encountered.

These two scenarios (Tables 5.1 and 5.3) demonstrate that when dealing with an infectious agent where a non-threshold model is assumed, where either the frequency of contamination (percentage of contaminated samples) or the extent of contamination (*L. monocytogenes* levels in a contaminated food) increases, then so does the risk and the predicted number of cases. Thus, if all RTE foods went from having 1 CFU/serving to 1000 CFU/serving, the risk of listeriosis would increase 1000-fold (assuming a fixed serving size). Conversely, the effect of introducing into the food supply 10 000 servings contaminated with *L. monocytogenes* at a level of 1000 CFU/g could theoretically be compensated by removing from the food supply a single serving contaminated at a level of 10^7 CFU/g.

In interpreting these results and in attempting to predict the actual effect of a change in the regulatory limits for *L. monocytogenes* in RTE foods, one also has to take into account the extent to which deviations from established limits occur. The current example is based on data from the United States of America, where the current allowable limit for *L. monocytogenes* in RTE foods is effectively 0.04 CFU/g (1 CFU/25 g), a level that if consistently achieved would be expected to result in less than one case of listeriosis per year in the United States of America. However, the baseline level for the United States of America population was 2130 cases (Mead et al., 1999). Both the current risk assessment and the United States of America FDA/FSIS draft risk assessment (2001) indicate that a portion of RTE food contain a substantially greater number of the pathogen than the stated limit and that the public health impact of *L. monocytogenes* is, most probably, almost exclusively a function of the foods that greatly exceed the current limit. Thus, in addressing the question posed by CCFH, the current risk assessment indicates that increasing the level of *L. monocytogenes* in RTE foods from 0.04 to 1000 CFU/g would increase the risk of foodborne listeriosis, provided that the current rate of deviations above the established limit remained proportionally the same. However, it could also be asked whether public health could be improved if a less stringent microbiological limit for RTE foods resulted in a substantial decrease in the number of servings that greatly exceeded the established limit, e.g. if the change encouraged manufacturers to routinely screen for *L. monocytogenes* in the plant environment and to take appropriate remedial actions. Models developed during the current risk assessment could be used estimate the extent of control over deviations from established limits that would be needed to improve public health if regulatory limits were relaxed, provided that sufficient data on the rate and extent of deviations were available for individual RTE foods.

As a means of further examining this concept, a simple hypothetical "what-if" scenario was developed based on the information provided in Tables 5.2 and 5.3. It examines the impact that compliance with a microbiological limit (i.e. defect rates) has on public health. Two potential limits, 0.04 CFU/g and 100 CFU/g, were examined in conjunction with different defect rates, i.e. the percentage of servings that exceed the specified limit. As a means of simplifying the what-if scenario and dramatizing the impact of compliance, a single

level of *L. monocytogenes*, 10^6 CFU/g, was assumed for all "defective" servings. Thus, if a serving of food was in compliance, it had a level of *L. monocytogenes* at or below the specified microbiological limit based on the distribution of *L. monocytogenes* levels **(**Table 5.2**)** used to calculate the 100% compliance values depicted in Table 5.3. Conversely, if a serving of food was out of compliance, it was assumed to have a set level of *L. monocytogenes* of 10^6 CFU/g, or since the assumed serving size was 31.6 g, a consumed dose of 3.16×10^8 CFU. The predicted number of cases as a function of the percentage of defective servings is provided in Table 5.4.

As noted in Table 5.3, at 100% compliance the number of predicted cases for both limits is low, with an approximate 10-fold differential between the two microbiological limits. As expected, the number of predicted cases increases with an increasing frequency of defective servings. At defect rates >0.0001% a 10-fold increase in the defect rate results in an approximate 10-fold increase in the number of predicted cases, regardless of the microbiological limits (i.e. 0.04 CFU/g versus 100 CFU/g). It is interesting to note that based on the conditions and assumptions of this simple what-if scenario, the defect rate that yielded a value approximately equivalent to the baseline value of 2130 cases used in the FDA/FSIS draft risk assessment (2001) was 0.018%.

A more detailed consideration of compliance could be achieved by incorporation of distributions reflecting the levels of *L. monocytogenes* observed in variety of foods. However, such a detailed consideration of compliance rates was beyond the scope of the current risk assessment. Furthermore, the simple hypothetical what-if scenario presented adequately demonstrates key concepts related to how compliance rates can strongly influence the actual risk associated with a microbiological criterion. In fact, it could be argued that the rate of compliance is a more significant risk factor than the numeric value of the criterion within the range that CCFH asked the risk assessment team to consider. The what-if scenario also demonstrates the concept that a less stringent microbiological limit could lead to an improvement in public health if new criteria lead to a substantive decrease in defect rates. For example, the model (Table 5.4) predicts that if a microbiological limit of 0.04 CFU/g with a 0.018% defect rate (2133 cases) was replaced with a 100 CFU/g limit and a 0.001% defect rate (124 cases), the predicted result based on the scenario is an approximate 95% reduction in foodborne listeriosis.

Table 5.4 Hypothetical "what-if" scenario demonstrating the effect of "defect" rate on the number of predicted cases of foodborne listeriosis.

Assumed percentage of "Defective" servings[(1)]	**Predicted number of listeriosis cases[(2)]**	
	Initial standard of 0.04 CFU/g	Initial standard of 100 CFU/g
0	0.5	5.7
0.00001	1.7	6.9
0.0001	12.3	17.4
0.001	119	124
0.01	1185	1191
0.018	2133	2133
0.1	11837	11848
1	117300	117363

NOTES: (1) For the purposes of this scenario, all defective servings were assumed to contain 10^6 CFU/g.
(2) For the purposes of this scenario, an r-value of 5.85×10^{-12} was employed and a standard serving size of 31.6 g was assumed. In the case of the 100 CFU/g calculations, the defective servings were assumed to be proportionally distributed according to the number of servings within each cell concentration bin.

5.3 QUESTION 2

Estimate the risk for consumers in different susceptible population groups.

As noted in Section 5.2, listeriosis is primarily a disease of certain subpopulations with impaired or altered immune function (e.g. pregnant women and their fetuses, the elderly, individuals with chronic diseases, AIDS patients, individuals taking immunosuppressive drugs). Susceptibility varies within the broadly defined susceptible group (e.g. the risk of listeriosis appears to be less for pregnant women than transplant recipients). It has been estimated that various subpopulations may have a 20- to 2500-fold increased risk of acquiring listeriosis (FDA/FSIS, 2001; Marchetti, 1996). CCFH requested that the risk assessment team attempt to estimate the differences in the dose-response relations for the different subpopulations with increased susceptibility. While previous risk assessments had considered the relative susceptibility of the entire population at increased risk, versus the general population, these risk assessments did not develop the type of detailed comparisons of subpopulations with increased susceptibility requested by CCFH. Thus, the current risk assessment had to develop *de novo* a means for addressing the request.

The basic approach taken to developing the requested dose-response relations was to take advantage of epidemiological estimates of the relative rates of listeriosis for different subpopulations. These "relative susceptibility" values were generated by taking the total number of listeriosis cases for a subpopulation and dividing it by the estimated number of people in the total population that have that condition. This value is then divided by a similar value for the general population. While there is a substantial uncertainty associated with these values (i.e. a relative susceptibility value is the ratio of two uncertain estimates and the exposures (diets) of the different subpopulations are assumed to be equivalent), it does provide a useful estimate of the differences in the susceptibility among the different subpopulations and the role that immune status has in determining an individual's risk from *L. monocytogenes* (Table 5.5).

Relating the relative susceptibility values to the dose-response relations for the different subpopulations requires a means of converting these point estimates to a dose-response curve. The unique characteristics of the exponential model allowed this to be done. Being a single parameter model, the exponential model allows the entire dose-response curve to be generated once any point on the curve is known. Thus, the r-value for an exponential dose-response curve can be estimated for a subpopulation using a relative susceptibility ratio and a reference r-value for the general population. Using the relative susceptibility value for cancer patients as an example (Table 5.5), the equation for the relative susceptibility is:

$$\text{Relative susceptibility} = RS = P_{cancer}/P_{healthy} = [1 - \exp(-r_{cancer}*N)]/[1 - \exp(-r_{healthy}*N)]$$

where P_{cancer} and $P_{healthy}$ denote the probability of systemic listeriosis for a cancer patient and a healthy adult, respectively, when exposed to a dose N of *L. monocytogenes*, and where r_{cancer} and $r_{healthy}$ are the r-values of exponential dose-response relationships specific for those population sub-groups.

This equation can be rearranged to:

$$r_{cancer} = - \ln [RS * \exp(-r_{healthy}*N) - (RS - 1)]/N$$

As long as the value for N, the number of *L. monocytogenes* consumed, is much smaller than the maximum assumed dose, the above relationship can be used to estimate the $r_{subpopulation}$ value. Using the above equation, the r-values for different classes of patients were estimated based on epidemiological data from France (Tables 5.5) and the United States of America (Table 5.6).

Table 5.5 r-values (exponential dose-response model) for different susceptible populations calculated using relative susceptibility information from France. Relative susceptibilities for the different subpopulations are based on the incidence of listeriosis cases (outbreak and sporadic) in these groups in 1992.

Condition	Relative susceptibility	Calculated r-value[(1)]	Comparable outbreak r-value
Transplant	2 584	1.41×10^{-10}	Finland butter 3×10^{-7}
Cancer – Blood	1 364	7.37×10^{-11}	
AIDS	865	4.65×10^{-11}	
Dialysis	476	2.55×10^{-11}	
Cancer – Pulmonary	229	1.23×10^{-11}	
Cancer – Gastrointestinal and liver	211	1.13×10^{-11}	
Non-cancer liver disease	143	7.65×10^{-12}	
Cancer – Bladder and prostate	112	5.99×10^{-12}	
Cancer – Gynaecological	66	3.53×10^{-12}	
Diabetes, insulin dependent	30	1.60×10^{-12}	
Diabetes, non-insulin dependent	25	1.34×10^{-12}	
Alcoholism	18	9.60×10^{-13}	
Over 65 years old	7.5	4.01×10^{-13}	
Less than 65 years, no other condition (reference population)	1	5.34×10^{-14}	

NOTES: (1) The r-value assumed for the reference population – "Less than 65 years, no other medical condition" – was 5.34×10^{-14}, which is the median of the r-value calculated assuming a maximum level of 8.5 $\log_{10}$ CFU per serving.

SOURCE: Marchetti, 1996.

Table 5.6 Dose-response curves for different susceptible populations calculated using relative susceptibility information from the United States of America. Relative susceptibilities for the different sub-populations are based on the incidences of listeriosis cases (outbreak and sporadic) in these groups.

Condition	Relative susceptibility	Calculated r-value[(1)]	Comparable outbreak r-value
Perinatal	14	4.51×10^{-11}	Los Angeles cheese 3×10^{-11}
Elderly (60 years and older)	2.6	8.39×10^{-12}	
Intermediate-age population (reference population)	1	5.34×10^{-14}	

NOTES: (1) The r-value assumed for the reference population – "Intermediate-age population" – was 5.34×10^{-14}, which is the median of the r-values calculated under the assumption of a maximum level of 8.5 $\log_{10}$ CFU per serving.

SOURCE: FDA/FSIS, 2001.

Comparison of the relative susceptibility values and corresponding r-values are consistent with the physiological observation that as an individual's immune system is increasingly compromised, the risk of listeriosis at any given dose increases and this is reflected in a corresponding increase in the r-value of the dose-response curve. The most compromised group in the French data, transplant patients, has an r-value approximately 4 orders of magnitude greater than the reference population (i.e. individuals less than 65 years old with no other medical conditions). The relative susceptibility values for the elderly population showed close agreement, 7.5 and 2.6 for the French and United States of America data, respectively. The differences reflect, in part, the different definitions of the age corresponding to the category "elderly" and the reference population. The United States of America intermediate-age population includes the patients that are separated out from the less-than-65-years-of-age group in the French data and the two reference populations are not expected, therefore, to have the same r-values. Nevertheless, the two tables indicate the magnitude of the impact that the impairment of the immune system by the specific conditions and disease states has on susceptibility to listeriosis.

The two outbreak r-values provide an indication of the validity of the models. The r-value for the Los Angeles outbreak in pregnant women from consumption of Hispanic cheese was very close to that estimated (Table 5.6). The r-value for the Finland outbreak from butter in hospitalized transplant patients differed from the values based on transplant patients by 1000-fold (Table 5.5). This may have resulted from the smaller number of individuals exposed, the extremely compromised and highly variable immunological status of the population, or the involvement of a highly virulent strain of *L. monocytogenes*. There is a clear need in future outbreaks for exposure levels, immune status of the patients and strain characteristics to all be investigated so that these dose-response models can be further refined and validated.

5.4 QUESTION 3

Estimate the risk from L. monocytogenes *in foods that support growth and foods that do not support growth at specific storage and shelf-life conditions.*

L. monocytogenes growth on foods is not the only determinant of risk of listeriosis. Additional factors that affect the risk associated with any food, regardless of whether it does or does not support *L. monocytogenes* growth, include:

- frequency of contamination;
- level of contamination;
- frequency of consumption; and
- susceptibility of consuming population.

This question suggests a number of alternative approaches to a simple growth/no-growth evaluation, such as a consideration of the effect on consumer risk of limiting the storage temperature and shelf-life of a product that supports the growth of *L. monocytogenes*. The risk assessment team has attempted to also consider these approaches while formulating its answer to the question.

As was discussed in the response to Question 1 (Section 5.2), it is possible that a food that does not permit the growth of *L. monocytogenes* but that is frequently contaminated at moderate levels could pose a greater risk than a food infrequently contaminated, or contaminated at low levels, but that does support growth of *L. monocytogenes.* Also, as noted previously, it is clear that an increase in the *total* numbers of *L. monocytogenes* in a food (whether through growth or increased frequency of contamination) will lead to increased consumer risk because, for *L. monocytogenes*, the dose-response model used indicates that public health risk is proportional to total number of *L. monocytogenes* in the food when consumed. Furthermore, as bacterial growth is exponential, the risk might be expected to increase exponentially with storage time.

Three approaches for answering this question are provided:

(i) general consideration of the impact of the ingested dose on the risk of listeriosis;

(ii) comparison of four foods that were selected, in part, to evaluate the effect of growth on risk; and

(iii) comparison of what-if scenarios for the foods evaluated that do support *L. monocytogenes* growth if they did *not* support *L. monocytogenes* growth. Each of the approaches is discussed below.

5.4.1 Growth rates in foods

L. monocytogenes is able to grow in many RTE foods, even if stored under appropriate refrigeration conditions. Factors affecting the growth of *L. monocytogenes* in foods are discussed in detail in Section 3.5. These include product formulation, storage time and temperature, and interactions with other microorganisms present in the product. In vacuum-packed foods, lactic acid bacteria can reach stationary phase without causing product spoilage. This can slow, or even prevent, the subsequent growth of *L. monocytogenes*. Table 5.7 presents representative generation times for different products as a function of product type and storage temperature. For every three generations of growth, there is

approximately a 10-fold increase in the bacterial population. As discussed in Section 5.2, a 10-fold increase in the levels of *L. monocytogenes* ingested produces a corresponding 10-fold increase in risk to human health. Thus, the risk from a food that supports the growth of *L. monocytogenes* increases with increasing storage time. However, the degree that the risk increases is dependent on the extent of growth in the food, which, in turn, is largely a function of *L monocytogenes'* growth rate in the food and the storage duration and conditions.

L. monocytogenes has been reported to grow in foods at temperatures as low as 0°C, water activities as low as 0.91–0.93 and pH as low as 4.2 (see Table 3.1). Combinations of suboptimal levels reduce the growth rate and can prevent growth at less extreme conditions than any of these factors acting alone. This principle, often referred to as hurdle technology or combination treatment, is exploited in food processing to prevent or limit the growth of bacteria in RTE foods.

The potential extent of growth varies among different foods, depending on the pathogen's growth rate in a specific food, which is a function of the product's composition and storage conditions, and on shelf-life of the product. From Table 5.7 it is evident that the growth of *L. monocytogenes* within the normal shelf-life of products could be substantial. For example, fresh cut vegetables have a relatively short shelf-life and do not support as rapid growth of *L. monocytogenes* as some other foods, such as milk or deli-meats. Thus, it would be expected that extent of growth in fresh cut vegetables would not be as great as those in other foods, resulting in a lower risk for given initial contamination rates and levels.

The example of the effect of storage time and temperature on the growth of *L. monocytogenes* and the subsequent risk of listeriosis can be considered a worst-case scenario in that it only considers the effect of temperature on generation times. Additional factors that act to delay the initiation of growth of *L. monocytogenes* (e.g. consideration of the lag phase), reduce the rate of growth (e.g. modified-atmosphere packaging), or suppress the maximum level reached by *L. monocytogenes* (e.g. growth of lactic acid bacteria) would decrease the extent of growth within a specified period of a product's shelf-life, with a corresponding decrease in risk. The actual calculation of risk would also have to consider that different servings would be consumed at various times within the total product shelf-life, as typically only a small fraction of a product is consumed near the end of its declared shelf-life.

5.4.2 Comparison of four foods

As discussed above, the four foods evaluated in the risk assessment (milk, ice cream, cold-smoked fish, and fermented meat products) were selected, in part, to compare the effect of various product characteristics on growth. This included specific consideration of the ability of foods to support growth. Thus, milk and ice cream were compared because they have similar compositions, servings sizes, frequencies of consumption, and rates and extents of initial contamination. However, milk supports *L. monocytogenes* growth while ice cream does not. Similarly, cold-smoked fish and fermented meat products have similar rates of initial contamination, serving sizes and frequencies of consumption, but the former supports the growth of *L. monocytogenes* while the latter does not.

Table 5.7 Representative generation times (hours) and growth potential of *Listeria monocytogenes* at different temperatures and shelf lives at 5°C in various RTE foods.

Temperature (°C)	Generation time (hours)			
	Milk	Vacuum-packed cold-smoked fish	Vacuum-packed processed meats	Sliced vegetables
5[(1)]	27.6	46.6	29.6	111
(95% confidence interval)	(14–226)	(20–infinite)	(14–infinite)	(28–infinite)
5[(2)]	25–30	40–49	16–48	–
10[(2)]	5–7	8–11	7–10	–
25[(2)]	0.7–1.0	1.2–1.7	1- 1.6	–
	Growth potential[(3)]			
5	~2–3	~4–5	~8–9	~0.3
	Advisory shelf-life (weeks)			
5	1–2	4–6	6–8	1

NOTES: (1) Values based on data collated in FDA/FSIS, 2001.
(2) Representative predictions and ranges from several published predictive models developed for growth rate of *L. monocytogenes.* No predictions were possible for vegetables because none of the published models were developed, or validated, for use with sliced vegetables.
(3) Log increase ignoring lag phase or suppression of growth by lactic acid bacteria.

Comparisons of the predicted risk per million servings (Table 4.34) between milk and ice cream, and cold-smoked fish and fermented meat products, indicate that the ability of a product to support growth within its shelf-life can increase substantially the risk of that product being a vehicle for foodborne listeriosis. Thus, the predicted risk per million servings of milk was approximately 100-fold greater than that for ice cream, and the risk for cold-smoked fish was approximately 10 000-fold greater than the corresponding risk for fermented meat products.

5.4.3 What-if scenarios

One of the useful features of a quantitative risk assessment is that the underlying mathematical models can be modified to allow various what-if scenarios to be run to evaluate the likely impact of different risk management options. Accordingly, a limited number of what-if scenarios were evaluated for milk and cold-smoked seafood, the two foods that supported the growth of *L. monocytogenes* and considered in the risk assessment. The results of these analyses were then compared to the predicted baseline risks to determine the impact of the intervention.

5.4.3.1 Milk

The initial assessment of risk associated with recontaminated pasteurized milk considered the likely growth of *L. monocytogenes* during the shelf-life of the product (see Section 4.2), using Canadian consumption characteristics as an example. To help answer CCFH Question 3, the model was re-executed after being modified so that the effect of growth was ignored, i.e. no growth during storage was modelled. The results of the two calculations were then compared to estimate the effect of growth on risk (Table 5.8).

The results suggest that an approximately 1000-fold increase in risk can be attributed to the predicted growth of *L. monocytogenes* in pasteurized milk by either measure of risk, i.e. risk per 1 million meals or risk per 100 000 population. The uncertainty measures associated

with the comparison suggested that the predicted increase in risk attributable to growth could be as little as 100-fold, or as much as >10 000-fold.

Several what-if scenarios were calculated for milk to illustrate the interactions of the various factors in determining the risks (Table 5.9). In one scenario, if all milk was consumed immediately after purchase at retail, the risks per serving and cases per population in both susceptible and healthy populations would decrease approximately 1000-fold. In contrast, if the contamination levels of milk were truncated at 100 CFU/g at retail but with growth still allowed, the incidence of listeriosis is predicted to be reduced by only about 70%. Two scenarios examined the impact of storage temperatures and times. When the temperature distribution was shifted so the median increased from 3.4 to 6.2°C, the mean number of illnesses increased over 10-fold for both populations. When the storage time distribution was shifted from a median of 5.3 days to 6.7 days, the mean rate of illnesses increased 4.5-fold and 1.2-fold for the healthy and susceptible populations, respectively.

5.4.3.2 Smoked Fish

The assumptions used with the cold-smoked fish model differ slightly from those used with the pasteurized milk example. The cold-smoked fish model also considers the effect of the growth of indigenous lactic acid bacteria in the product, which, when they grow to high numbers, suppress the growth of *L. monocytogenes* (see Section 4.5). The extent of that growth suppression is not known with certainty. In the baseline model, two assumptions concerning the growth rate suppression by lactic acid bacteria were tested. In the what-if scenario the growth rate inhibition of *L. monocytogenes* by the lactic acid bacteria was set to zero. Table 5.10 compares the risk estimates when growth was modelled to occur or not, including the effect of different assumptions about the magnitude of the inhibition of *L. monocytogenes* growth rate due to the growth of lactic acid bacteria.

Table 5.8 Estimates of the increase in risk of listeriosis from growth during storage of pasteurized milk between purchase and consumption.

	Normal-risk population		**High-risk population**		**Mixed population**	
	Mean	(s.e.)[a]	Mean	(s.e.)	Mean	(s.e.)
With growth (baseline model)						
Cases per 100 000 population	1.6×10^{-2}	(5.0×10^{-4})	5.2×10^{-1}	(3.1×10^{-2})	9.1×10^{-2}	(4.7×10^{-3})
Cases per 1 000 000 servings	1.0×10^{-3}	(1.0×10^{-4})	2.2×10^{-2}	(9.0×10^{-4})	5.0×10^{-3}	(2.0×10^{-4})
Without growth						
Cases per 100 000 population	1.3×10^{-5}	(6.7×10^{-8})	3.8×10^{-4}	(1.6×10^{-6})	6.7×10^{-5}	(2.4×10^{-7})
Cases per 1 000 000 servings	5.9×10^{-7}	(3.1×10^{-9})	1.7×10^{-5}	(7.5×10^{-8})	3.6×10^{-5}	(1.4×10^{-8})
Increased risk with growth relative to that without growth (n-fold increase)						
Cases per 100 000 population	1 231		1 366		1 358	
Cases per 1 000 000 servings	1 695		1 294		139	

KEY: s.e. = Standard error of the mean.

Table 5.9 Three what-if scenarios that illustrate the impact of contamination and storage on the estimated risks of listeriosis per 100 000 population and per 1 000 000 servings for milk under typical conditions of storage and use.

Food	Estimated mean cases of listeriosis per 100 000 people	Estimated mean cases of listeriosis per 1 000 000 servings
Milk baseline	9.1×10^{-2}	4.6×10^{-3}
No growth	6.7×10^{-5}	
With contamination truncated at 100 CFU/g	2.8×10^{-2}	
Increase storage temperature (from 3.4 to 6.2°C)	1.2×10^{0}	
Increase storage time (from 5.3 to 6.7 days)	2.0×10^{-1}	

With either assumption concerning the effect of lactic acid bacteria on *L. monocytogenes* growth potential, growth greatly increased the risk of listeriosis. Assuming that 80 to 100% suppression occurred, it allowed more growth than the assumption of 95% growth rate suppression, a result of the faster overall growth rate after lactic acid bacteria have achieved maximum population growth. The risk per serving and cases per 100 000 population increased 700- to 1000-fold in the first assumption (80–100% growth rate suppression) and 67- to 85-fold under the latter assumption (95%) from the "no *L. monocytogenes* growth" to the baseline (growth) scenarios.

For the cold-smoked fish model, between 15 and 20% of the population were assumed to be in the high-risk category, but the cases attributable to the normal and high-risk categories were not estimated discretely. Rather, as in the previous example, the predicted number of cases is a weighted mean of the normal and high-risk populations. It is known that the population with increased susceptibility to listeriosis experiences between 80 and 98% of total reported cases of listeriosis. Also, in this example, no attempt to differentiate consumption between these two susceptibility classes was made, unlike that undertaken in the assessment of milk (Section 4.2). These differences do not affect the interpretation of the results with a food but some caution must be exercised in comparing the impact of growth on the risk *between* the foods. However, the differences in the modelling are relatively minor and the predicted increase in risk due to growth in the two examples is roughly comparable. For example, in the case of pasteurized milk (Table 5.9), the modelling also suggests that the increase in risk due to the growth of *L. monocytogenes* within the normal shelf-life of the product is between approximately 100- and 1000-fold, similar to the risk increase predicted for cold-smoked fish due to *L. monocytogenes* growth during storage.

A further what-if scenario was performed to estimate the effect on risk of reducing the shelf-life of smoked fish by 50%. This was tested by replacing the original shelf-life distribution of 1–28 days, with a most likely value of 14 days, by a shelf-life distribution of 1–14 days, with a most likely value of 7 days. The effect of this change resulted in an 80% reduction in the predicted increase in risk due to growth. The fact that the change was not greater is probably due to the effect of lactic acid bacteria, which is modelled to begin to suppress *L. monocytogenes* growth after approximately 3 weeks of storage at 5°C (see Section 4.5.3.7).

Table 5.10 Impact of the growth of *Listeria monocytogenes* during storage of cold-smoked fish between purchase and consumption on the risk of listeriosis under typical conditions of storage and use.

Growth rate inhibition due to growth of lactic acid bacteria	Cases per 1 000 000 meals		Cases per 100 000 population	
	No Growth	Growth Modelled	No Growth	Growth Modelled
80–100%	4.51×10^{-4}	4.59×10^{-1}	9.60×10^{-5}	6.57×10^{-2}
	(3.09×10^{-5})[(1)]	(3.29×10^{-1})	(1.07×10^{-5})	(3.78×10^{-2})
Difference[(2)]		1020-fold		684-fold
95%		3.82×10^{-2}		6.48×10^{-3}
		(1.96×10^{-2})		(2.26×10^{-3})
Difference[(2)]		85-fold		67-fold

NOTE: (1) Values in parentheses are standard deviations. (2) Increase in risk of listeriosis in the growth versus the no-growth scenarios

5.4.4 Summary

Three different approaches were taken to demonstrate the effect of growth of *L. monocytogenes* on the risk of listeriosis associated with RTE foods. It is apparent that the potential for growth strongly influences risk, though the extent of that increase is dependent on the characteristics of the food and the conditions and duration of refrigerated storage. However, using the examples provided in the risk assessment, the ability of these RTE foods to support the growth of *L. monocytogenes* appears to increase the risk of listeriosis on a per-serving basis by 100- to 1000-fold over what the risk would have been if the foods did not support growth. While it is not possible to present a single value for the increased risk for all RTE foods because of the different properties of the various foods, the range of values here provide some insight into the magnitude of the increase in risk that may be associated with the ability of a food to support the growth of *L. monocytogenes.*

Part 6.

Key findings and Conclusions

This risk assessment reflects the state of knowledge on listeriosis and on contamination of foods with *L. monocytogenes* when the work was undertaken, in 2002. It provides an insight into some of the issues to be addressed in order to control the problems posed by *L. monocytogenes,* and approaches for modelling a system to evaluate potential risk management options. It addresses the specific questions posed by the CCFH and provides a valuable resource for risk managers in terms of the issues to be considered when managing the problems associated with *L. monocytogenes,* and alternative or additional factors or means to consider when addressing a problem.

A number of important findings have come out of this work. Firstly, the probability of illness as a result of consuming a specified number of *L. monocytogenes* is appropriately conceptualized by the disease triangle, where the food matrix, the virulence of the strain and the susceptibility of the consumer are all important factors. However, little information was found on food matrix effects for *L. monocytogenes*. In animal studies the impact of strain variation on virulence has been shown to be large, but it is not currently possible to determine the human virulence for any individual strain and explicitly include that in the model. However, the epidemiologically-based models used in the risk assessment implicitly consider the variation in virulence among strains. Population-based models were developed that estimate the likelihood of illness for various immunocompromised human populations after consuming specified numbers of *L. monocytogenes*. Although the maximum levels of contamination at consumption are uncertain, different models based on different values all lead to the same general findings.

An important finding of the risk assessment was that, based on the predictions of the models developed, nearly all cases of listeriosis result from the consumption of high numbers of the pathogen. Conversely, the models predict that the consumption of low numbers of *L. monocytogenes* has a low probability of causing illness. Old age and pregnancy increase susceptibility and thus the risk of acquiring listeriosis when exposed to *L. monocytogenes*. Likewise, diseases and medical interventions that severely compromise the immune system greatly increase the risks. The risk of acquiring listeriosis from the consumption of contaminated food appears to be adequately described by the type of "probabilistic statement" that underlies the exponential dose-response relationship used in the risk assessment, namely, that there is a finite, albeit exceedingly small, possibility that a case could occur if an unusually susceptible consumer ingested low numbers of an unusually virulent strain

The data used in this risk assessment came from a number of different countries, although these were predominantly industrialized countries. Based on this available data there is no

evidence that the risk from consuming a specific number of *L. monocytogenes* varies from one country to another for the equivalent population. Differences in manufacturing and handling practices in various countries may affect the contamination pattern and therefore the risk per serving for a food. The public health impact of a food can be evaluated by both the risk per serving (considers the frequency of contamination and the distribution of contamination levels within that particular food), and the annual number of cases per population (considers the number of servings of the food consumed by the population and the size of that population). A food may have a relatively high risk per serving but, if a minor component of the national diet, it may have a relatively small impact on public health as defined by the number of cases per year attributable to that food. Conversely, a food that has a relatively small risk per serving but that is consumed frequently and in large quantities may account for a greater portion of the cases within a population.

With regard to the outcome of the modelling work undertaken, this risk assessment indicates that control measures that reduce the frequencies of contamination with *L. monocytogenes* bring about proportional reductions in the rates of illness, provided the proportions of high contaminations are reduced similarly. Control measures that prevent the occurrence of high levels of contamination at consumption would be expected to have the greatest impact on reducing the rates of listeriosis. Contamination with high numbers of *L. monocytogenes* at manufacturing and retail is rare, and foods such as ice cream and fermented meat products that do not permit growth during storage have relatively low risks per serving and low annual risks per population. In foods that permit growth during storage, particularly if stored at higher temperatures or for longer duration, the low numbers of *L. monocytogenes* at manufacture and retail may increase during storage to levels that represent substantially elevated relative risks of causing listeriosis.

Although high levels of contamination at retail are relatively rare, improved public health could be achieved by reducing these occurrences at manufacture and retail in foods that do not permit growth. In foods that permit growth, control measures, such as better temperature control or limiting the length of storage periods, will reduce the increase in risk that occurs due to growth of *L. monocytogenes*. Re-formulating foods so they do not support growth would be expected to also reduce the occurrence of high doses and thus reduce the risk of listeriosis.

Finally, based on the risk assessment it is concluded that the vast majority of cases of listeriosis are associated with the consumption of foods that do not meet current standards for *L. monocytogenes* in foods, whether the standard is zero tolerance or 100 CFU/g. Raising a zero tolerance standard to a higher value (e.g. changing the standard from 1 CFU/25 g to 100/g) would be expected to result in increased incidence of listeriosis. However, if by relaxing the standard, there was a greater level of compliance with that standard through the improved adoption of control measures that significantly decreased the incidence of RTE food servings that exceeded the standard, particularly the number of servings with elevated levels of *L. monocytogenes,* then increasing the standard would actually have a positive impact on public health.

While this risk assessment has documented a number of important findings and addressed specific risk management questions from Codex it is not without its weaknesses. It is important that these are recognized, acknowledged and documented. This facilitates better understanding of the risk assessment as well as its correct interpretation and use. Transparency in this area can actually help minimize the weaknesses. There are a number of

limitations and caveats to this current risk assessment that the end user should be aware of so that he/she can make optimal use of the work in the appropriate manner. These are outlined below.

- The risk assessment focuses on four RTE foods and only examines them from retail to consumption. This limits the application of the risk assessment particularly with regard to the consideration of risk management options at the primary production and processing stages.
- The risk characterization results are subject to uncertainty associated with a modelled representation of reality involving simplification of the relationships among prevalence, cell number, growth, consumption characteristics and the adverse response to consumption of some number of *L. monocytogenes* cells. However, the modelling is appropriate to quantitatively describe uncertainty and variability related to all kinds of factors and attempts to provide estimates of the uncertainty and variability associated with each of the predicted levels of risk.
- The amount of quantitative data available on *L. monocytogenes* contamination was limited and restricted primarily to European foods.
- Data on the prevalence and number of *L. monocytogenes* in foods came from many different sources, which adds to uncertainty and variability. Also, assumptions had to be made with regard to distribution of the pathogen in foods.
- The data used for prevalence and cell numbers may not reflect changes in certain commodities that have occurred in the food supply chain during the past ten years.
- The consumption characteristics used in the risk assessment were primarily those for Canada or the United States of America.
- The r-values and their distributions were developed using epidemiological data on the current frequency of *L. monocytogenes* strain diversity observed, with their associated virulence. If that distribution of virulence were to change (as reflected by new epidemiological data), the r-values would have to be re-calculated.
- There is uncertainty associated with the form of the dose-response function used, and with the parameterization. Also, the dose-response section of the hazard characterization is entirely a product of the shape of the distribution of predicted consumed doses in the exposure assessment component of the *Listeria* risk assessment undertaken in the United States of America (FDA/FSIS, 2001). Therefore its validity is dependant on the validity of the FDA/FSIS exposure assessment, and changes to that exposure assessment should lead directly to changes in the parameter, r.
- Predictive modelling was used to model the growth of *L. monocytogenes* in RTE foods, between the point of retail and the point of consumption, and the exposure assessment was based on information derived from those models. It is known that models may overestimate growth in food, and so reliance on such a model can result in an overestimation of the risk.

While the available data were considered adequate for the current purposes, the risk assessment could be improved with additional data of better quality for every factor in the

assessment. The uncertainty ranges about the risks per serving and number of cases in a population indicate the effect of data gaps on the estimates.

Consumption data were usually determined for nutritional purposes and lack critical information relevant to microbial quality. Contamination data were often neither recent, systematic, quantitative nor representative for different countries. In particular, the frequencies of high levels of contamination need to be better known. Additional knowledge on modelling growth would improve the estimates of the levels of *L. monocytogenes* consumed. Specific areas include the maximum levels of growth, interactions with the indigenous spoilage flora (including the lactic acid bacteria), distributions of storage times, and interactions of storage times and temperatures with spoilage.

The dose-response models are all based upon pairing population consumption patterns with epidemiological statistics. Improved investigation of outbreaks to determine the food involved, the amount of food consumed, number of *L. monocytogenes* consumed, the number of people exposed, number of people ill, the immunological status of all exposed people, and the virulence properties of the causative strain together would eventually lead to more accurate and specific dose-response models.

New data is constantly becoming available, but in order to complete this work it was not possible to incorporate the very latest data in the risk assessment. A future iteration of the work would incorporate such new data

This risk assessment reflects the current state of knowledge about the contamination of foods with *L. monocytogenes* and rates of listeriosis. Implementation of systematic surveys to determine the handling, consumption and contamination of foods would improve future risk assessments. Research to further the understanding of microbial growth dynamics would increase the ability to estimate final levels of contamination. More complete investigation of outbreaks and determination of the virulence characteristics of *L. monocytogenes* will make the dose-response relationships more accurate and precise. Nevertheless, the dose-response models used in the current risk assessment should be applicable to all countries. Conversely, the exposure assessments are unique to each country and depend upon specific data on the factors that affect that population's exposure.

This risk assessment did not attempt to evaluate the factors that lead to the contamination of a food at retail. Additional product pathway exposure assessments for selected foods would provide additional understanding of how these foods become contaminated and the factors that have the greatest impact on preventing or eliminating that contamination. Creating valid product pathway assessments would then permit testing the impact on the incidences of listeriosis of various mitigations or postulated effects of regulatory changes. The critical factor in evaluating the risk from a food is the frequency distribution of the levels of contamination when that food is consumed. Estimating the actual effect of a proposed regulatory programme or risk mitigation strategy on this distribution is highly uncertain, yet determining the resulting change in the distribution is fundamental to reducing the occurrence of listeriosis.

This risk assessment should improve our overall understanding of the issue *L monocytogenes* in foods and associated listeriosis and it is anticipated that it can therefore pave the way for risk management action to address this problem at the international level.

Part 7

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Appendices

Appendix 1. Glossary of Terms

Beta distribution

The Beta distribution is defined as

$$f(x) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} x^{\alpha-1}(1-x)^{\beta-1},$$

where $0 \le x \le 1$, $\alpha > 0$ and $\beta > 0$. There are generalizations to a random variable defined on any interval [a, b].

(Source: http://www.statsoft.com/textbook/glosfra.html)

Binomial distribution

The binomial distribution is used when each trial has exactly two mutually exclusive possible outcomes, often labelled success and failure. The binomial distribution is the probability of obtaining x successes in N trials where the probability of success on a single trial is π. The binomial distribution assumes that π is fixed for all trials. The formula for the binomial probability mass function is

$$p(x;n,\pi) = \binom{n}{x} \pi^x (1-\pi)^{n-x}, \text{ for } x = 0, 1, 2, \ldots, n>0.$$

(Source: www.itl.nist.gov/div898/handbook/eda/section3/eda366h.htm)

Confidence interval

A range of values believed to include an unknown population parameter. Associated with the interval is a measure of the confidence we have that the interval contains the parameter of interest, the *confidence level*, (depending on interpretation) the probability that the parameter of interest will fall within the specified confidence interval. Where a point estimate is a specific numerical value that estimates a parameter, an interval estimate such as a confidence interval is a numeric range that estimates a parameter, generally with an associated probability. A confidence interval for a parameter generalizes to a *confidence set* for more than one parameter at a time. (Source: www2.spsu.edu/tmgt/richardson/Statistics/)

It should be noted that, under the frequentist definition, the confidence level is the probability of the interval covering the true unknown value. The true value is fixed and it is the interval that is random in repeated experimentation.

Continuous random variable

A continuous random variable is one that takes an infinite number of possible values. Continuous random variables are usually measurements. Examples include height, weight,

and the concentration of *L. monocytogenes* in a sample. Examples of probability distributions for continuous random variables are the Normal distribution and the Gamma distribution.

(Source: www.stats.gla.ac.uk/steps/glossary/)

Correlation

Correlation is a measure of the relation between two or more variables. Correlation coefficients can range from -1 to +1. The value of -1 represents a perfect negative correlation while a value of +1 represents a perfect positive correlation. A value of 0 represents a lack of correlation.

(Source: www.statsoft.com/textbook/stathome.html)

Convolution

Consider X and Y are non-negative, independent, integer-valued random variables with probability distributions $Pr\{X=j\}=a_j$ and $Pr\{Y=j\}=b_j$ and $Pr\{X=y, Y=k\}=a_jb_k$. The sum S=X+Y is a random variable also, and we recognize that the event S=r is the union of events (X=0, Y=r), (X=1, Y=r-1), …, (X=r, Y=0). So, the probability distribution for S is $Pr\{S=r\}=c_r$ where $c_r=a_0b_r + a_1b_{r-1} + \ldots + a_rb_0 = \sum_{k=0}^{r} a_kb_{r-k}$. Feller (1968: 266 et ff.) names this operation convolution (German *Faltung*, French *composition*) and extends the definition to any 2 sequences $\{a_k\}$ and $\{b_k\}$, not necessarily probability distributions. Combinations like this appear in much of the simulation.

Deterministic

Commonly, *deterministic* is an antonym for *stochastic.*

Discrete random variable

A discrete random variable is one which may take on only a countable number of distinct values such as 0, 1, 2, 3, 4, ... Discrete random variables are usually, but not necessarily, counts. If a random variable can take only a finite number of distinct values, then it must be discrete. Examples of discrete random variables include the number of children in a family, the Friday night attendance at a cinema, the number of *L. monocytogenes* organisms in a serving of food. Examples of probability distributions for discrete random variables are the Binomial distribution and the Poisson distribution.

(Source: www.stats.gla.ac.uk/steps/glossary/)

Distribution function

The distribution of a variable is a description of the relative numbers of times each possible outcome in the domain of the variable will occur in a number of trials. The function describing the distribution is called the probability function (probability mass function if the random variable takes only discrete values; probability density function if the random variable is continuous). The *cumulative distribution function* describes the probability that a trial takes on a value less than or equal to a number, commonly $F(x) = Pr\{X \leq x\}$. The cumulative distribution function is monotone increasing whereas the probability density is not. (Source: mathworld.wolfram.com)

Empirical distribution function

Given data $\{x_k, k = 1, \ldots, n\}$ sorted from smallest to largest, $\{x_{(k)}, k = 1, \ldots, n\}$, $x_{(1)} \le x_{(2)} \le \ldots \le x_{(n)}$, the empirical (cumulative) distribution function (e.c.d.f. or e.d.f.) is the function

defined by $\hat{F}(x) = \frac{number\ of\ x_k \le x}{n}$, a step function with steps of size $1/n$. The values

of the e.c.d.f. are the discrete set of cumulative probabilities $\{0, 1/n, \ldots, n/n\}$. When used in a simulation, values between any two consecutive samples, $x_{(k)}$ and $x_{(k+1)}$ cannot be simulated, nor can a value smaller than the minimum, nor can a value larger than the maximum. The e.c.d.f. has mean equal to the sample mean, and variance equal to $(n\text{-}1)/n$ times the sample variance. The e.c.d.f. tends to underestimate the true mean and variance when the underlying distribution is skewed to the right. Expected values of simulated e.c.d.f. quantiles are equal to the sample quantiles. Some variations on the e.c.d.f. appear in simulations: linearly extrapolating between observations; or adding lower and upper tails to the data to reflect a range of the variable outside the observed range, either through expert judgement or by postulating some shape to the tails beyond the sample extremes.

Gamma distribution

The probability density of the Gamma distribution is defined as

$$f(x) = x^{\alpha-1} e^{-x/\beta} [\beta^{\alpha} \Gamma(\alpha)]^{1},$$

where $x \ge 0$, $\alpha > 0$, $\beta > 0$. α is referred to as the shape parameter. β is referred to as the scale parameter. For integral α, one can recognize the Gamma distribution as the distribution of the waiting time for α Poisson events. As a special case, when $\alpha = 1$, the Gamma distribution is the Exponential distribution.

(Source: www.statsoft.com/textbook/glosfra.html)

Latin Hypercube Sampling

Latin Hypercube Sampling (LHS) is a stratified sampling technique where the random variable distributions are divided into equal probability intervals. A probability is randomly selected from within each interval for each basic event. Generally, LHS will require fewer samples than simple Monte Carlo sampling for similar accuracy. LHS ensures that the entire range of each variable is sampled.

(Source: http://saphire.inel.gov/guest_area/SAF00758.htm)

Lognormal distribution

The lognormal distribution has the probability density function

$$f(x) = \frac{1}{[x\sigma\sqrt{2\pi}]} \exp\left(-\frac{1}{2}[\ln x - \mu]^2 / \sigma^2\right),$$

where $0 \le x < \infty$, $\mu > 0$, $\sigma > 0$. If the distribution of a random variable X is lognormal, then the distribution of ln(X) is Normal.

(Source: www.statsoft.com/textbook/glosfra.html)

Maximum likelihood

The method of maximum likelihood is a general method of estimating parameters of a population by values that maximize the *likelihood* (*L*) of a sample. The likelihood *L* of a sample of n observations $x_1, x_2, ..., x_n$, is the joint probability function $p(x_1, x_2, ..., x_n)$ when $x_1, x_2, ..., x_n$ are discrete random variables. If $x_1, x_2, ..., x_n$ are continuous random variables, then the likelihood *L* of a sample of *n* observations, $x_1, x_2, ..., x_n$, is the joint density function $f(x_1, x_2, ..., x_n)$. When *L* is a function of parameters, then the maximum likelihood estimates (m.l.e.) of the parameters are the values that maximize *L*.

(Source: www.statsoft.com/textbook/stathome.html)

Method of moments

This method can be employed to determine parameter estimates for a distribution. The method of matching moments sets the distribution moments equal to the data moments and solves to obtain estimates for the distribution parameters. For example, for a distribution with two parameters, the first two moments of the distribution (the mean μ and variance σ^2 of the distribution) would be set equal to the first two moments of the data (the sample mean and variance, e.g. the unbiased estimators $\dot{x}$ and s^2) and solved for the parameter estimates.

(Source: www.statsoft.com/textbook/glosfra.html)

Monte Carlo

In Monte Carlo methods, the computer uses random number simulation techniques to mimic a statistical population. For each Monte Carlo replication, the computer: simulates a random sample from the population; analyses the sample; and stores the result. After many replications, the stored results will mimic the sampling distribution of the statistic.

(Source: www.statsoft.com/textbook/stathome.html).

Normal distribution

A continuous random variable X has a Normal distribution if its probability density function is $f(x) = \frac{1}{\sqrt{2\pi}\sigma} \exp(-\frac{(x-\mu)^2}{\sigma^2})$, $-\infty<x<\infty$, $\sigma>0$, $-\infty<\mu<\infty$. The normal probability density function has two parameters: μ (mean) and σ (standard deviation). The Normal distribution is sometimes called the *Gaussian* distribution.

(Source: http://ce597n.www.ecn.purdue.edu/CE597N/1997F/students/
michael.a.kropinski.1/project/tutorial#Normal Distribution)

Quantile

The p^{th} quantile of a distribution of values is a number x_p such that a proportion *p* of the population values are less than or equal to x_p. In a simple random sample of *n* values, where the sample values ordered in ascending order are $x_{(1)}, \ldots, x_{(n)}$, it is common to use the $x_{(k)}$ as an estimate of the $k/(n+1)^{th}$ quantile, although different software packages use variations of this, $(k-\alpha)(n-\alpha-\beta)^{-1}$ for $\alpha,\beta>0$ (Hyndman and Fan, 1996).

(Source: www.statsoft.com/textbook/glosfra.html)

Quantitative risk assessment

If "risk assessment is generally regarded as a process to scientifically evaluate the probability and severity of known or potential adverse effects attributable to a hazardous agent, process or circumstance" (Cassin et al., 1998), then quantitative risk assessment "implies an estimation of the probability and impact of adverse health outcomes…" (Cassin et al., 1998).

Poisson distribution

The Poisson distribution is defined as $Pr\{X=k\} = \mu^k e^{-\mu}/k!$, x = 0, 1, …, where $\mu>0$ is the average number of occurrences (count) per interval. A Poisson random variable X is a count, interpreted in the context of either distance, area, volume, time or other measure of size (interval) as follows:

- Each non-overlapping interval increment of interest is so small that only one event can occur within it (or at least, the probability of 2 or more events in the interval is negligible), but the sum of the individual increments comprises the entire interval or time period; and
- the probability of an event occurring in the given increment is constant. The number of events observed depends only on the length of the interval considered and not on its end points. If length of interval is 0 and time is 0, the number of events observed is 0. The numbers of changes in non-overlapping intervals are independent for all intervals.

Examples occur in many fields: the number of imperfections (gas trap or cracks) per square metre in rolls of metals; the number of telephone calls per hour received by an office; the number of cashews per can in one can of mixed nuts; the number of bacteria in a given culture; or the number of typing errors per page. The specified region can be an area, a volume, a segment of a line or even a piece of material.

(Sources: http://engineering.uow.edu.au/Courses/Stats/File40.html
http://mathworld.wolfram.com/PoissonDistribution.html)

Rank Correlation

A rank correlation coefficient is a correlation coefficient that is based on the ranks of the sample values and not the actual values. A rank is a consecutive number assigned to a specific observation in a sample of observations sorted by their values. So, ranks reflect the ordered relation of one observation to the others in the sample. The lowest value is assigned a rank of 1; the higher ranks represent the higher values.

(Source: www.statsoft.com/textbook/stathome.html)

Simulation

Etymology: Middle English *simulation*, from Middle French, from Latin simulation-, *simulatio*, from *simulare*

1. the act or process of simulating. 2. a sham object. 3a. the imitative representation of the functioning of one system or process by means of the functioning of another <*a computer simulation of an industrial process*>. 3b. examination of a problem often not subject to direct experimentation by means of a simulating device.

See also: Monte Carlo. (Source: Merriam-Webster Collegiate Dictionary On-line. www.m-w.com/cgi-bin/mweb)

Stochastic

Etymology: Greek *stochastikos* skilful in aiming, from *stochazesthai* to aim at, guess at, from *stochos* target, aim, guess.

- RANDOM; specifically: involving a random variable <a stochastic process>
- involving chance or probability: PROBABILISTIC <a stochastic model of radiation-induced mutation>.

(Source: Merriam-Webster Collegiate Dictionary On-line. http://www.m-w.com/cgi-bin/mweb)

A stochastic process is a family of random variables X(t) indexed by a parameter t, which usually takes values in the discrete set $T = \{0, 1, 2, \ldots\}$ or the continuous set $T = [0, +\infty)$. In many cases t represents time, and X(t) is a random variable observed at time t. Examples are the Poisson process, the Brownian motion process, and the Ornstein-Uhlenbeck process. Considered as a totality, the family of random variables $\{X(t), t \varepsilon T\}$ constitutes a "random function".

(Source: www.britannica.com/bcom/eb/article/3/0,5716,117323+26+109439,00.html)

Commonly, *deterministic* is an antonym for *stochastic*.

NOTE: A more extensive glossary of terms related to microbiological risk assessment can be found in MRA 3, an earlier volume in this series (FAO/WHO, 2003).

REFERENCES CITED IN THE GLOSSSARY OF TERMS

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Hyndman, R.J. & Fan, Y. 1996. Sample quantiles in statistical packages. *American Statistician*, **50**: 361–365.

Cassin, M.H., Lammerding, A.M., Todd, E.C.D., Ross, W. & McColl, R.S. 1998. Quantitative risk assessment for *Escherichia coli* O157:H7 in ground beef hamburgers. *International Journal of Food Microbiology*, **41**: 21–44.

FAO/WHO. 2003. Hazard characterization for pathogens in food and water: Guidelines. *FAO/WHO Microbiological Risk Assessment Series*, No. 3. 61p.

Appendix 2. Simulation modelling for the four risk assessment examples

A2.1 INTRODUCTION

This appendix serves as documentation for the simulation modelling carried out for the pasteurized milk and ice cream examples, making the work transparent. The model documentation reflects methodological issues, but is not intended to explain the issues in detail. Specific issues related to the development of the two risk assessment models are addressed here. These include a description of the consumption characteristics used and the modelling of home storage conditions, and how non-susceptible and susceptible populations might be defined. How to combine independent data sets to describe prevalence of *L. monocytogenes* in foods and to describe concentration of *L. monocytogenes* in foods are also addressed. The appendix provides a list of references to support the documentation here, and to provide that vast amount of supplementary material that is the background for much of the work. Still other methodological material appears in the main body of the report (Part 3 – Exposure assessment, and Part 4 – Example risk assessments). Implementation of the Monte Carlo simulation for this exposure assessment was performed using Analytica™1.11, 2.0.1 or 2.0.5 (Lumina Decisions) software. Additional computations and preparation of graphs were done using Microsoft® Excel 97 and Microsoft® Excel 2000, and with S-Plus 4.5 Professional, S-Plus 2000 Professional and S-Plus 6 Professional (MathSoft, Inc.).

A2.2 MODELLING THE EXPOSURE ASSESSMENT

A2.2.1 Overview

Objectives for the exposure assessment are to simulate the number of *L. monocytogenes* organisms in a serving of a particular RTE) food, *Lm ingested*, and to determine the annual frequency of servings for individuals in the consuming population, *Annual meals*. Every shape in the influence diagram (Figure A2.1) is termed a node. Different shaped nodes perform different functions. The hexagonal figures, *Lm ingested* and *Annual meals*, represent the stochastic results that answer the questions deriving from the objectives. Elliptical shapes, such as *Food amount eaten*, are chance (stochastic) nodes that hold intermediate calculations that form part of the modelling for the objective nodes. The round-cornered rectangular nodes, such as *Prevalence and concentration*, are organizing modules that contain other nodes. The hexagonal pennant boxes, *Discrete distributions* and *Study indices* are libraries of functions that support some calculations or that contain index nodes that structure the results. Arrows indicate influences and indicate the direction of the influence. For example, the number of *L. monocytogenes* organisms ingested in a serving when that number exceeds zero, *Lm ingested given >0*, depends on the *Concentration in ingested food* and the *Food amount eaten*. The values in *Food frequency* determine what values reside in *Annual meals*.

To model the exposure assessment, the following information is needed:

1. *Prevalence and concentration characteristics*, measured at the same consistent point in the farm-to-fork chain. Prevalence relates how often the food is contaminated with *L. monocytogenes*. The notion is generalized to consider it equivalent to the probability that a serving from a package or unit of product contains any contamination. Concentration defines how many *L. monocytogenes* organisms are in a contaminated portion.
2. *Storage characteristics* and *Growth characteristics* that determine the amount of *Growth* of *L. monocytogenes* in the product from that point in the process to the point of consumption.
3. *Consumption characteristics* that relate how much food consumers eat and how often they eat it. How large a serving the consumer eats determines how many *L. monocytogenes* organisms the consumer ingests.
4. *Non-susceptible and susceptible populations*. Hazard Identification generally indicates that some portions of the consuming population are more susceptible to infection or illness from *L. monocytogenes*.

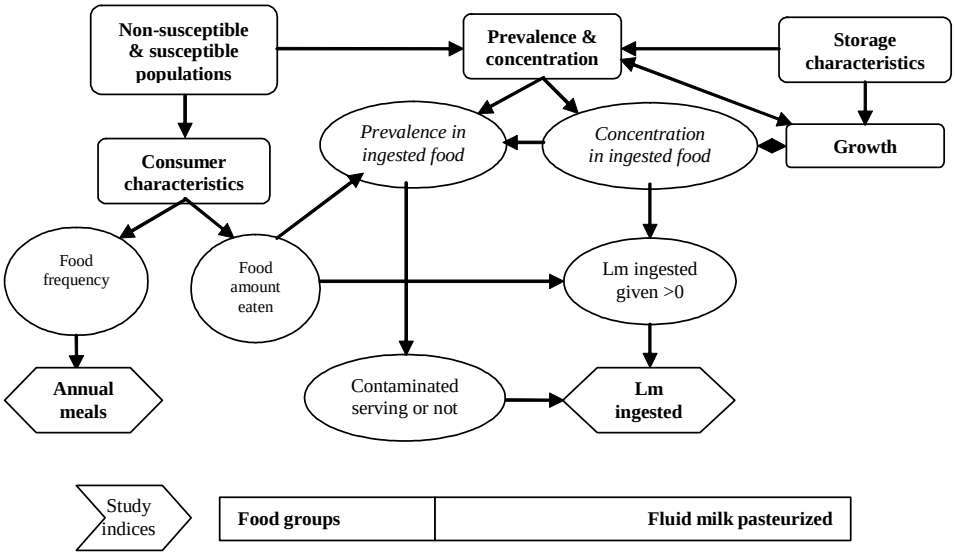

Figure A2.1 Influence diagram for *Listeria monocytogenes* exposure assessment.

Figure A2.1 clarifies the model structure and what information is needed from the exposure assessment. However, it does not make explicit the node's specific parameterization. Also, it does not show all of the interrelationships and dependencies. Accompanying documentation in this Appendix does that (such as Table A2.1), and specific methodological issues are addressed in the various sections.

Table A2.1 Nodes for top level of *Listeria monocytogenes* in RTE eat foods exposure assessment model.

Title Identifier Structure	Description and Definition
Non-susceptible and susceptible populations Nonandsusceptible Module	Module holds characteristics that define the allocation of individuals from Gender × Age groups to non-susceptible and susceptible groups. Among adults, for whom we have some information about consumption characteristics, susceptible groups are defined to include all adults 65 and older, pregnant women (1.3% of the population) and individuals with suppressed immune systems and certain medical conditions such as cancer and recent organ transplantation (3.3% of the population) (Miller, Whiting and Smith, 1997).
Consumption characteristics Consumption_character Module	Consumption characteristics come from 24-hour recall data from CFPNS (1992–1995), which addressed the nutritional habits of non-institutionalized adults between 18 and 74 years old in Québec, Nova Scotia, Saskatchewan, Alberta and Prince Edward Island.
Prevalence and concentration Prevalence_and_conce Module	Prevalence and concentration module determines simulated distributions for the prevalence of *L. monocytogenes* in food and the concentration in contaminated food, nominally at retail.
Storage characteristics Storage_characterist Module	Storage characteristics module determines simulated distributions for the refrigerator temperature that the consumer stores the food at, and the length of time, measured as if from retail purchase, to the time of consumption.
Growth Growth2 Module	Growth module determines growth characteristics for *L. monocytogenes* in the food. Growth is characterized by exponential growth rates and stationary phase population size for each foodstuff.
Food amount eaten Serving_size1 (g) Chance node	Food amount eaten is the simulated distribution of the daily serving size for individuals from the non-susceptible group and for individuals from the susceptible group. Food amount eaten comes directly from the consumption amounts generated in the Consumption characteristics module.
Annual meals Annual_meals Objective node	The number of Annual meals for an individual is calculated from the Food frequency probability of consumption on a given day, by implementing Binomial sampling. The number of meals (population days with consumption) is calculated in the Consumption characteristics module, rounded here for display Table(Annualmealsreporting)(Round(Binomial(365, Mealfrequency[Annualmealsreporting='Individual'])), Round(Mealfrequency[Annualmealsreporting='Population']))
Prevalence in ingested food Prevalence_in_ingest Chance node	The Prevalence in ingested food node is the simulated distribution for how often a serving contains any L. monocytogenes contamination. For Icebox:=Refrigerator_studies Do For Person:=Risk_group_definitio Do Correlatedprevalence * (1-Exp(-10^Finalconcentration[Refrigerator_studies=Icebox] * Serving_size1[Risk_group_definitio=Person]))
Contaminated serving or not There_or_not_there Chance node	Contaminated serving or not is a simple accounting of whether a serving is contaminated or not. It is generated by sampling from the outcomes Not contaminated and Contaminated, with probabilities Not contaminated (1-Prevalence_in_ingest) Contaminated Prevalence_in_ingest

Title Identifier Structure	Description and Definition
Concentration in ingested food Finalconcentration (log_{10} CFU/g) Chance node	Concentration in ingested food is the simulated distribution of the concentration of *L. monocytogenes* in contaminated food at ingestion. Initial concentrations grow into final concentrations according to the growth determined in the Growth module. Final concentrations are restricted to theoretical maximum population densities or stationary phase densities. Using Calculatedfinal:= Initialconcentration + Unconstrgrowthamount Do (if Maximum_population >0 then (if Calculatedfinal <= logten(Maximum_population) then Calculatedfinal else logten(Maximum_population)) else Calculatedfinal)
Lm ingested given >0 Dose (CFU) Chance node	The Lm ingested given >0 node records the simulated distribution of the number of *L. monocytogenes* organisms in a serving of food, in those cases where the number of organisms is larger than 0. The Prevalence in ingested food node lets us derive how often the number of organisms is 0. Lm ingested given >0 generates non-zero observations by sampling on [1,∞) with Poisson probabilities. For Icebox:=Refrigerator_studies Do For Person:=Risk_group_definitio Do logten(Round(Conditional_poisson(10^Finalconcentration[Refrigerator_studies=Icebox] * Serving_size1[Risk_group_definitio=Person])))
Lm ingested Lm_ingested (CFU) Objective node	Lm ingested is one of the objective nodes for this exposure assessment. It is calculated by combining the simulated distributions for the Prevalence in ingested food and the Lm ingested given >0. The number of *L. monocytogenes* organisms ingested when the food is not contaminated is assumed to be 0. For temp:=Run Do if There_ot_not_there[Run=temp]='Not contaminated' then 0 else 10^Dose
Study indices Row_and_column_inde1 Library	Study indices is a collection of index information that structure the results.

A2.2.2 Non-susceptible and susceptible populations

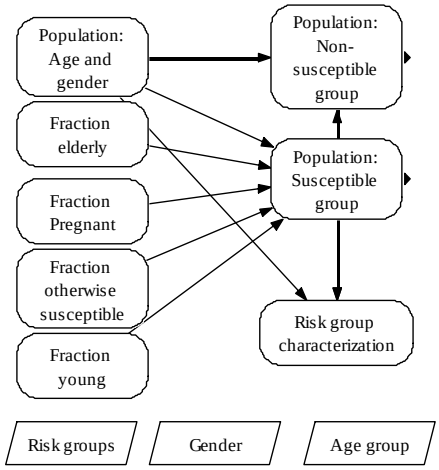

Figure A2.2 Influence diagram for non-susceptible and susceptible populations.

The susceptible population is determined by the fractions of persons who have one of the characteristics named: elderly, pregnant, otherwise susceptible, young. For the present implementation of the exposure assessment, where there are no consumption data for persons under 18 years old from Canadian data (CFPNS, 1992–1995), the fraction young is moot. In Figure A2.2, *Population age and gender* table holds domain estimates for the Age and Gender groups used. For Canadian consumption data, estimates represent the population counts, in the years of the surveys, in five provinces: Alberta, Nova Scotia, Prince Edward Island, Quebec and Saskatchewan, for which consumption information is available (CFPNS, 1992–1995). *Fraction elderly*, *Fraction pregnant*, *Fraction otherwise susceptible*

and *Fraction young* are tables that describe the fraction of the population, in Gender × Age groups, who would be attributed to the susceptible group, for the named reason. For example, a fraction of Females, 18–34 and 35–49 would be attributed to the susceptible group in the *Fraction pregnant* table. All persons 65 and older, but no others, would be attributed to the susceptible group in the *Fraction elderly* table. Allocations were based on Miller, Whiting and Smith (1997), as applied to the Canadian population. The *Population susceptible group* table collects the fractions together to give the population size in the susceptible group, by Gender and by Age. The *Population non-susceptible group* table is derived by difference from the *Population age and gender* and *Population susceptible group* tables to give the population size in the non-susceptible group, by Gender and by Age. *Risk group characterization* is a useful summary of the attribution of individuals to the non-susceptible and susceptible groups. This module is also a natural holding place for parallelogram-shaped index nodes, *Risk groups*, *Gender* and *Age group*, that structure the results through many modules in the model. Details of the nodes are described in Table A2.2.

Table A2.2 Nodes for non-susceptible and susceptible populations module.

Title, Identifier, Structure	Description and Definition
Population Age and gender Popn_age_gender Module	Population age and gender table holds domain estimates for the Age and Gender groups used.
Fraction elderly Fraction_elderly Variable node	Fraction elderly, Fraction Pregnant, Fraction otherwise susceptible and Fraction young are tables that describe the fraction of the population, in Gender × Age groups, whom we would attribute to the susceptible group, for the named reason.
Fraction Pregnant Fraction_pregnant Variable node	
Fraction otherwise susceptible Fraction_otherwise_s Variable node	
Fraction young Fraction_young Variable node	
Population non-susceptible risk group Population_normal Variable node	Population non-susceptible group table is derived by difference from the Population Age and gender and Population Susceptible group tables to give the population size in the non-susceptible group, by Gender and by Age. Popn_age_gender — Population_high_risk
Population susceptible group Population_high_risk Variable node	Population susceptible group table collects the fractions together to give the population size in the susceptible group, by Gender and by Age. Popn_age_gender * (Fraction_elderly + Fraction_otherwise_s + Fraction_pregnant + Fraction_young)
Risk group characterization Riskgroupcharacteriz Variable node	Risk group characterization is a useful summary of the attribution of individuals to the risk groups.
Risk groups Risk_group_definitio Index node	Risk groups are defined as ['Non-susceptible', 'Susceptible']
Gender Gender_definition Index node	Gender is defined as ['Female', 'Male']
Age group Age_group_definition Index node	Age group is defined as ['18-34', '35-49', '50-64', '65-74']

A2.2.3 Consumption characteristics

Consumption characteristics are the amount of food eaten in a serving, the daily probability of consuming the food and the annual number of meals (days with consumption) in the population. The nodes *Food amount eaten* and *Food frequency* are collectors for the characteristics calculated in each of the food-specific modules: *Ice cream*; and *Fluid milk, pasteurized*. *Food amount eaten* is the distribution of amounts eaten (g). *Food frequency* is the probability of consuming the food on a given day. *Survey results* and *Ecdf columns* are index nodes that structure data tables in the *Fluid milk, pasteurized* and *Ice cream* modules (Table A2.3, Figure A2.3). Exposure assessment examples for pasteurized milk and ice cream were implemented using the modules described here.

Table A2.3 Nodes for Consumption characteristics module.

Title, Identifier, Structure	Description and Definition
Ice cream Consumption_char1 Module	The main consumption characteristics are the serving size and the frequency of consumption for ice cream.
Fluid milk, pasteurized Consumption_char3 Module	The main consumption characteristics are the serving size and the frequency of consumption for pasteurized fluid milk.
Food amount eaten Serving_size (g) Chance node	Food amount eaten is the distribution of amounts eaten (g). DetermTable(Food_groups)(Samp_cons_ice, Samp_cons_pmilk)
Food frequency Meal frequency Chance node	Food frequency is the probability of consuming the food on a given day and the annual meals (population consumption days) for population. Determtable(Food_groups, Annualmealsreporting)(Samp_freq_ice, Annualmealsicecream, Samp_freq_pmilk, Annualmealspmilk)
Survey results Survey_results Index node	Survey results structures data tables in Fluid milk, pasteurized and Ice cream modules. ['Respondents', 'Consumers']
Ecdf columns Ecdf_columns Index node	Ecdf columns structures data tables in Fluid milk, pasteurized and Ice cream modules. ['Amount', Fraction']

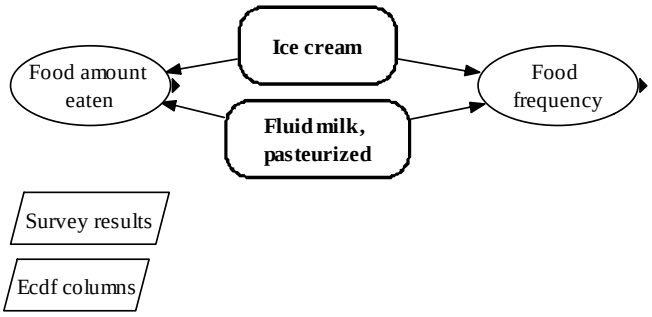

Figure A2.3 Influence diagram for *Consumption characteristics* module.

A2.2.4 *Ice cream* and *Fluid milk, pasteurized* modules

Consumption characteristics modules are specific to the RTE food considered. The structure of consumption characteristics modules for *Ice cream* and for *Fluid milk, pasteurized* are identical. Both are described together, referring to the *Fluid milk, pasteurized* example (Table A2.4, Figure A2.4).

Table A2.4 Nodes for *Ice cream* and for *Fluid milk, pasteurized* modules.

Title, Identifier, Structure	Description and Definition
Gender, age consumption frequency Gender_age_freq6 Variable node	Gender, age consumption frequency is a table indexed by Age group and Gender, holding point estimates of daily consumption probabilities for Pasteurized milk. Other nodes in the module use the point estimates to determine what proportions of Age and Gender group characteristics to include in non-susceptible and susceptible populations.
Susceptible group proportions Gender_age_pro_high6 Variable node	Susceptible group proportions is a table that holds proportions of total eating episodes assigned to Gender and Age group for individuals in the susceptible group. We have adjusted Gender, age consumption frequency proportions to reflect membership in susceptible groups, Population: susceptible group.
Susceptible group gender Sampled_high_risk_g6 Chance node	Susceptible group gender and Susceptible group age are stochastic nodes that hold a Gender and an Age Group, sampled so that Gender × Age group proportions among consumers in the susceptible population are respected.
Susceptible group age Sampled_high_risk_a6 Chance node	
Non-susceptible group proportions Normal_intake_pr6 Variable node	Non-susceptible group proportions is a table that holds proportions of total eating episodes assigned to Gender and Age group for individuals in the non-susceptible group. We have adjusted Gender, age consumption frequency proportions to reflect membership in non-susceptible groups, Population: Non-susceptible group.
Non-susceptible group gender Sampled_gender6 Chance node	Non-susceptible group gender and Non-susceptible group age are stochastic nodes that hold a Gender and an Age Group, sampled so that Gender × Age group proportions among consumers in the non-susceptible population are respected.
Non-susceptible group age Sampled_age_group6 Chance node	
Nutrition survey results, milks Nutrition_survey_re6 Variable node	Nutrition survey results, milks is a table that holds inferential statistics from the nutrition surveys: the number of survey respondents and the number who reported consuming Pasteurized milk on a given day.
Pasteurized milk amounts Pmilk_amount Variable node	Pasteurized milk amounts is a table that holds empirical daily Pasteurized milk amounts collected from the nutrition surveys. The table has columns Amount, an amount consumed (g) and Fraction, the inverse of the design-based weights associated with Pasteurized milk consumers in the nutrition surveys. There is a separate table for each Gender × Age group.
Milk amount index Pmilk_amount_index Index node	Milk amount index structures the table of amounts, Pasteurized milk amounts. Range of sequence corresponds to a set of rows in an Excel spreadsheet. Sequence(5, 459, 1)
Beta, milks frequency Beta_frequency6 Chance node	Beta, milks frequency uses a Beta distribution to represent uncertainty or variability over a Gender × Age group, for consumers' consumption probability on a given day. Beta, milks frequency is assumed to be Beta(x+1, n-x+1), where n is the number of respondents, and x is the estimated number of Pasteurized milk consumers, $n\pi$.

Title, Identifier, Structure	Description and Definition
Annual meals, susceptible group Annualmealshighrisk6 Chance node	Annual meals, susceptible group simulates the annual meals (population days with consumption) in susceptible population. It incorporates the variability and uncertainty about the fraction of adults who consume Pasteurized milk on a given day. It samples binomially among population days (population × 365), but uses a Normal approximation. We truncate the Normal distribution at 0 and the total population days. Sum(Sum(Using Beta_value:= Beta_frequency6[Risk_group_definitio='High risk'] Do Using People_days:=Population_high_risk*365 Do Using Interim:= -Truncate(-(Truncate(Normal(People_days*Beta_value, People_days*Sqrt(Beta_value*(1-Beta_value))), 0)), -People_days) Do if Interim<=0 then 0 else if Interim>=People_days then People_days else Round(Interim), Gender_definition), Age_group_definition)

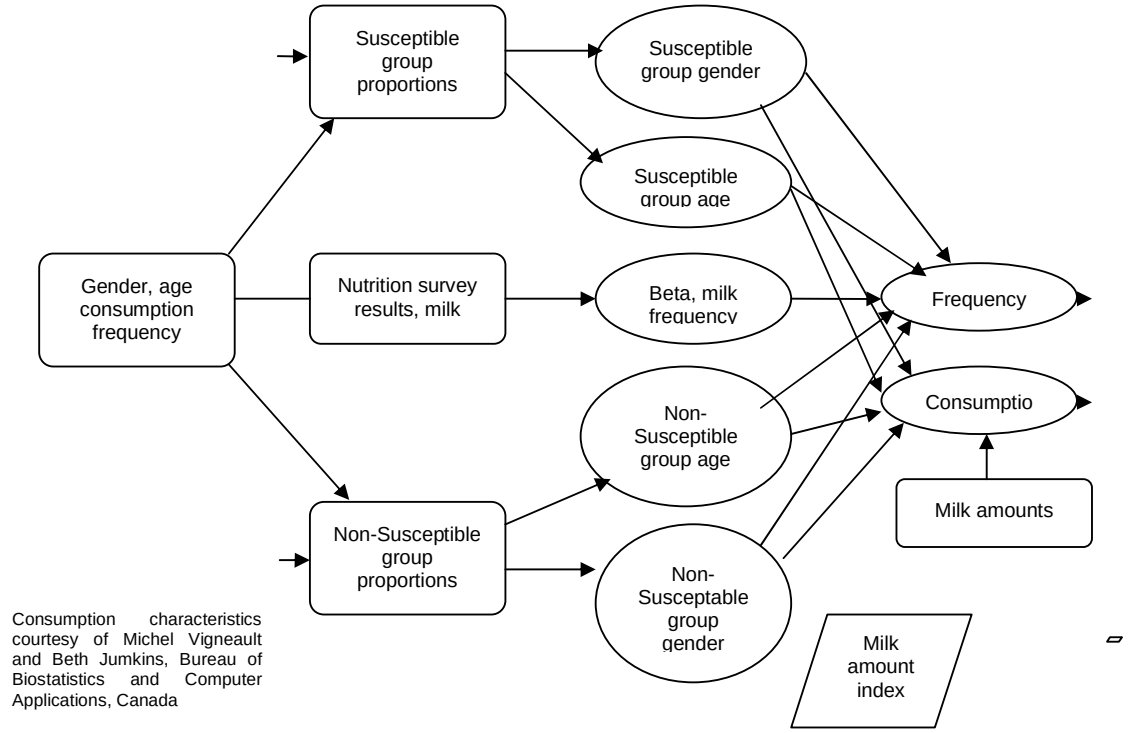

Figure A2.4 Influence diagram for *Pasteurized milk* consumption characteristics module. Except for changes to node identifiers, the *Ice cream* consumption characteristics module is identical.

A2.2.5 Prevalence and concentration

The *Prevalence and concentration* module simulates the *Prevalence characteristics* – nominally prevalence of *L. monocytogenes* contamination in foods at retail or source for the consumer – and simulates the *Concentration characteristics* – nominally the *L. monocytogenes* concentration in the food at that point. The module lets one specify a rank correlation coefficient between the prevalence and concentration. Last, it simulates the *Prevalence in ingested food* and the *Concentration in ingested food*, when the concentration is larger than 0 (Figure A2.5, Table A2.5).

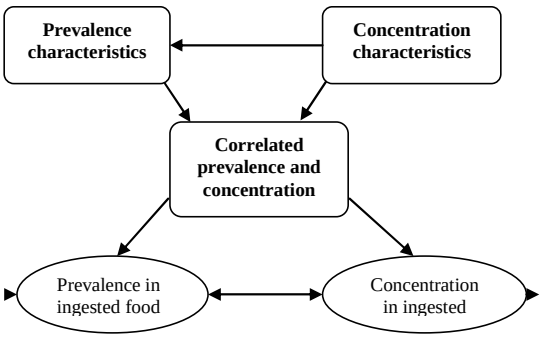

Figure A2.5 Influence diagram for *Prevalence and concentration* characteristics module.

Table A2.5 Nodes for *Prevalence and concentration* module.

Title, Identifier, Structure	Description and Definition
Prevalence characteristics Prevalence_character Module	Prevalence characteristics simulates the prevalence of *L. monocytogenes* as measured at retail, in the packages or units that the consumer would purchase.
Concentration characteristics Concentration_charac Module	Concentration characteristics simulates the *L. monocytogenes* concentration as measured at retail or source, in the packages or units that the consumer would purchase.
Correlated prevalence & concentration Correlated_prevalenc Module	Correlated prevalence & concentration is the means to specify the rank correlation coefficient between the prevalence and concentration.
Prevalence in ingested food Prevalence_in_ingest Chance node	The Prevalence in ingested food node is the simulated distribution for how often a serving contains any *L. monocytogenes* contamination. Some servings from a contaminated package will carry no organisms (exp(-mμ), where the serving size is mg and the concentration is μg^{-1}). Those probabilities adjust the prevalence estimates that emerge from the Prevalence and concentration characteristics module. Prevalence in ingested food is calculated as follows. For Icebox:=Refrigerator_studies Do For Person:=Risk_group_definitio Do Correlatedprevalence * (1-Exp(-10^Finalconcentration[Refrigerator_studies=Icebox] * Serving_size1[Risk_group_definitio=Person]))
Concentration in ingested food Finalconcentration (log_{10} CFU/g) Chance node	Concentration in ingested food is the simulated distribution of the concentration of *L. monocytogenes* in contaminated food at ingestion. Initial concentrations grow into final concentrations according to the growth determined in the Growth module. Final concentrations are restricted to theoretical maximum population densities or stationary phase densities. Using Calculatedfinal:= Initialconcentration + Unconstrgrowthamount Do (if Maximum_population >0 then (if Calculatedfinal <= logten(Maximum_population) then Calculatedfinal else logten(Maximum_population)) else Calculatedfinal)

A2.2.6 Prevalence characteristics

This implementation models prevalence as measured at retail, in the product packages or units that the consumer would purchase. The *Prevalence parameters* table specifies the α and β parameters of a Beta distribution. *Prevalence in packages* is defined as Beta (α, β) parameters as appropriate for each food group (Table A2.6).

Table A2.6 ***Nodes for Prevalence characteristics module.***

Title, Identifier, Structure	Description and Definition
Prevalence parameters Prevalenceparameters Variable node	The Beta distribution, which has support on [0, 1], is a common way to characterize the heterogeneity in the prevalence. Determtable(Food_groups,Prevdistrnparameters)(0.424, 0.55, 155.47)
Prevalence in packages Prevalenceinpackage Chance node	Prevalence in packages samples from the Beta distribution specified by Prevalence parameters and makes the Packaging adjustment required Packaging_adjustment * (Using localalpha:=Prevalenceparameters[Prevdistrnparameters='alpha'] Do Using localbeta:=Prevalenceparameters[Prevdistrnparameters='beta'] Do Beta(localalpha, localbeta))
Prevalence distribution parameters Prevdistrnparameters Index node	Prevalence distribution parameters indexes the columns of the Prevalence parameters table. ['alpha', 'beta']

A2.2.7 Concentration characteristics

Concentration distributions were derived from published studies for two groups of RTE foods. In Figure A2.6, rounded rectangular shapes are variables holding a table of data that describes the empirical distribution function or a set of quantiles, or parameters for a distribution function for the concentrations .

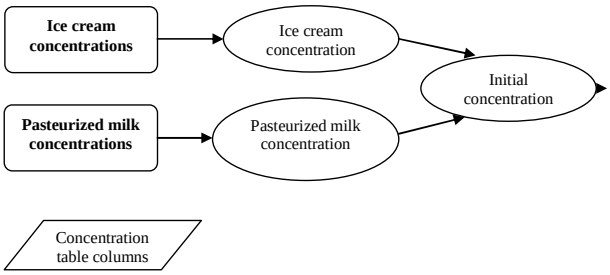

Figure A2.6 Influence diagram for *Concentration characteristics* module.

At each iteration, a value is sampled from the distribution and collected into one of the elliptical nodes. The *Initial concentration* node collects all results, still separate, together in the same place. The parallelogram at the bottom of the Figure A2.6, *Concentration table columns*, lists the columns that appear in concentrations tables: Concentration, and Quantile. Data collection and organization from referenced studies provide concentration distributions that represent levels of concentrations in recognizable packages or units of products (Table A2.7).

Table A2.7 Nodes for *Concentration characteristics* module.

Title, Identifier, Structure	Description and Definition
Ice cream concentrations Icecreamconctable Variable node	Ice cream concentrations holds quantile distribution for *L. monocytogenes* concentration in ice cream.
Ice cream concentration Icecreamconc Chance node	Ice cream concentration samples from the cumulative distribution that is specified in Ice cream concentrations. Cumdist(Icecreamconctable[Concentration_tables='Quantile'], Icecreamconctable[Concentration_tables='Concentration'])
Pasteurized milk concentrations Pastmilkconctable Variable node	Pasteurized milk concentrations holds quantile distribution for *L. monocytogenes* concentration in pasteurized milk
Pasteurized milk concentration Pastmilkconc Chance node	Pasteurized milk concentration samples from the cumulative distribution that is specified in Pasteurized milk concentrations. Cumdist(Pastmilkconctable[Concentration_tables='Quantile'], Pastmilkconctable[Concentration_tables='Concentration'])
Concentration table columns Concentration_tables Index node	Concentration table columns structures the concentration tables. ['Concentration', 'Quantile']
Initial concentration Initialconcentration Chance node	Initial concentration node collects all results, still separate, together in the same place. Determtable(Food_groups)(Icecreamconc, Pastmilkconc)

A2.2.8 Correlated prevalence and concentration

The Analytica™2.0.1 and 2.0.5 software does not directly implement built-in methods for generating random variables with a desired correlation structure. The installation does provide a Library module, *Correlated Distributions*, which provides the mechanics to achieve the desired result. The *Correlated Distributions* library module implements the method of Iman and Conover (1982), which makes the rank correlation between specified variables meet the desired result. So, *Prevalence in packages*, from the *Prevalence characteristics* module and *Initial concentration*, from the *Concentration characteristics* module, are re-ordered to produce rank-correlated *Correlated prevalence* and *Correlated concentration*.

A2.2.9 Storage characteristics

Storage temperature and *Storage time* characterize storage conditions in this exposure assessment. Storage temperature is intended to represent storage in the consumer's refrigerator, after purchase of the food product from retail. Storage time is intended to represent the length of time that the food product is stored at that temperature, measured from retail purchase until the consumer eats a portion. A simple implementation assumes constant temperature. More complicated implementations that depend on quantitative data lacking here could incorporate time and temperature integration.

Storage temperature comes from four separate sources in different countries, which were included through the whole exposure to examine the effects of different assumptions about temperatures, or different distributions of temperatures. It is assumed that refrigerator storage temperatures are the same for any food product – unrealistic, but simplifying (Table A2.8).

Table A2.8 Quantiles for refrigerator temperature (°C) distributions, showing point estimates for cumulative probabilities from four studies.

Audits International (2000)		**Johnson et al. (1998)**		**Sergelidis et al. (1997)**		**O'Brien (1997)**	
°C	Cum. Prob.	°C	Cum. Prob.	°C	Cum. Prob.	°C	Cum. Prob.
0	0	-2.5	0	0	0	0	0
0.14	0.03	-2	0.002	9	0.45	4	0.40
0.83	0.06	-1	0.002	10	0.75	11	1
1.94	0.15	0	0.01	13	1		
3.05	0.37	1	0.02				
4.16	0.74	2	0.07				
5.28	0.80	3	0.11				
6.39	0.91	4	0.18				
7.50	0.98	5	0.30				
8.61	0.99	6	0.44				
9.72	1.00	7	0.76				
10.28	1	8	0.92				
		9	0.96				
		10	0.99				
		11	0.997				
		12	0.998				
		13	1				

Storage time represents the length of time that the consumer stores the product before eating a serving from it. Storage time distributions are modelled as specific to the food product under consideration. Following FDA/FSIS (2001), *Minimum time*, *Mode time* and *Maximum time* parameterize storage time distributions, via Triangular(Minimum time, Mode time, Maximum time). Minimum time is set to a constant 0.5 days for all products, but Mode and Maximum are intended to depend on the food. Mode time and Maximum time are allowed to be stochastic. Mode time varies as Uniform(±20% nominal). Maximum time varies as Uniform(±50% nominal). Nominal values are listed in Table A2.9. Mode time and Maximum time are strictly related, so that nonsensical values are not generated. Consequently, this implementation calculates an *Indep. Storage time* that aligns the smallest *Mode time* with the smallest *Indep. Maximum* (Table 2.10).

Table A2.9

Post-retail storage times (days).

	Min	**Mode**	**Max**
Ice cream	0.5	7	30
Fluid milk, pasteurized	1	5	12

Storage life for pasteurized milk depends on the growth of spoilage bacteria, which depends on temperatures. The effect would be to truncate the time distribution differently at different temperature values. General tendencies would be the same. Distribution shapes would change. The storage life for pasteurized milk is assumed to be 12 days at 4°C, with storage life at other temperatures determined by the relationship $Life(T) = 12 \times \left[\frac{4+7.7}{T+7.7}\right]$ in Neumeyer, Ross and McMeekin (1997) and Neumeyer et al. (1997). The influence diagram is shown in Figure A2.7.

Table A2.10 Nodes for Storage characteristics module.

Title, Identifier, Structure	Description and Definition
Audit International 2000 Audit2000 Variable node	Audits International 2000 is 1 of 4 sources of refrigerator storage temperatures (Table A2.8).
Refrigerator characteristics Refrigerator Index node	Refrigerator characteristics node structures the data in the refrigerator temperature table. ['Temperature', 'Frequency', 'Cumulative frequency']
Refrigerator studies Refrigerator_studies Index node	Refrigerator studies node maintains a consistent list of the 4 refrigerator temperature source studies. ['Audits International 2000', 'Johnson et al., 1998', 'Sergelidis et al., 1997', 'O'Brien 1997']
Storage temperature Storage_temperature Chance node	Sstorage temperature is sampled from the information in the four refrigerator temperature studies. Cumdist(Audit2000[Refrigerator='Cumulative frequency'], Audit2000[Refrigerator='Temperature'])
Post-retail storage time Post_retail_storage_ Variable node	Post-retail storage time holds minimum, mode and maximum storage time for each Food groups label and for each Updates label. Storage time represents the length of time that the consumer stores the product before eating a serving from it. Storage time distributions are modelled as specific to the food product under consideration. Following FDA/FSIS (2001), Minimum time, Mode time and Maximum time parameterize storage time distributions, via Triangular(Minimum time, Mode time, Maximum time) (Table A2. 9).
Minimum time Minimumtime Chance node	Minimum time extracts the minimum time from Post-retail storage time appropriate to the selected Food groups. Post_retail_storage_[Post_retail_storage_='Minimum']
Mode time Modetime Chance node	Mode time extracts the nominal mode time from Post-retail storage time appropriate to the selected Food groups. Mode time varies as Uniform (±20% nominal). Using Temp:=Post_retail_storage_[Post_retail_storage_='Mode'] Do Uniform(0.8*Temp, 1.2*Temp)
Indep. maximum Maximumindeptime Chance node	Indep. maximum extracts the nominal maximum time from Post-retail storage time appropriate to the selected Food groups. Maximum time varies as Uniform(±50% nominal). Using Temp:=Post_retail_storage_[Post_retail_storage_='Maximum'] Do Uniform(0.5*Temp, 1.5*Temp)
Corr. Maximum Maximumtime Chance node	The Mode time is assumed to follow a Uniform(0.8*mode, 1.2*mode) and the Indep. maximum to follow a Uniform(0.5*maximum, 1.5*maximum). To avoid nonsensical parameter combinations, and to represent what would to be a sensible set of conditions, the random mode and random maximum have a correlation coefficient of 1. For Onebyone:=Updates Do Using Another:=Rank(Maximumindeptime[Updates=Onebyone],Run) Do Using Sortedmaximum:=Maximumindeptime[Updates=Onebyone, Run=Sortindex(Another,Run)] Do Sortedmaximum[Run=Rank(Modetime[Updates=Onebyone], Run)]
Storage time Preliminarytime Chance node	Storage time is the storage time before acting to make the time and temperature related. Triangular(Minimumtime, Modetime, Maximumtime)
Truncated storage time Storage_time Chance node	The storage life for pasteurized milk is assumed to be 12 days at 4°C, with storage life at other temperatures determined by the relationship in Neumeyer, Ross and McMeekin (1997) and Neumeyer et al. (1997). (Using local1 := (1643/((Storagetemperature+7.7)^2)) Do Using local2 := (Storage_time1>local1) Do ((Storage_time1*(1-local2))+(local2*For local3 := Run Do (If local2[Run=local3] Then (-Truncate((-Storage_time1),(-local1[Run=local3])))) Else 0))))

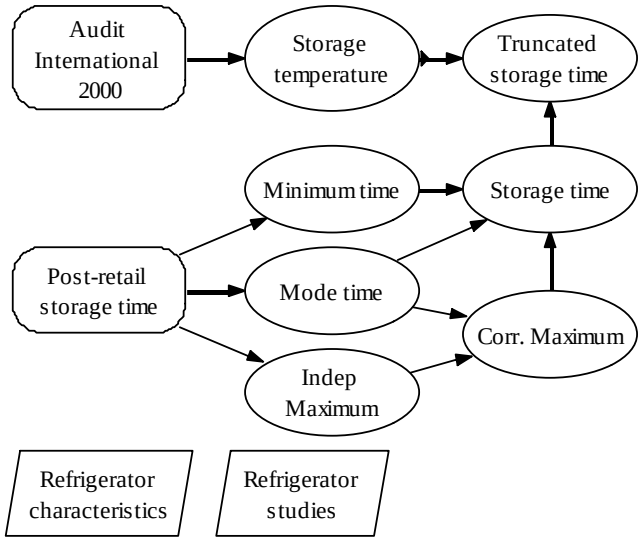

Figure A2.7 Influence diagram for *Storage characteristics* module.

A2.2.10 Growth

The *Growth* module uses simulated *Growth characteristics* to determine the *Growth per day* If it is assumed that every day, or every part day, has the same *Storage conditions* and the same *Growth characteristics*, then the *Unconstrained growth and die off* can be determined in a straightforward manner, constraining that *Unconstrained growth* by the stationary phase maximum population density. The influence diagram is shown in Figure A2.8 and the noted are described in Table A2.11.

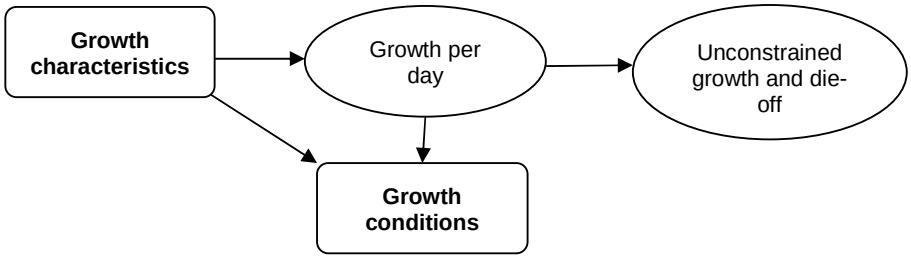

Figure A2.8 Influence diagram for *Growth* module.

Table A2.11 Nodes for *Growth* module.

Title, Identifier, Structure	Description and Definition
Growth characteristics Growth_characteristi Module	Growth characteristics are characterized by exponential growth rates at 5°C and stationary phase population size for each foodstuff.
Growth conditions Growth_conditions Module	Growth conditions summarizes the growth characteristics and growth conditions.
Unconstrained growth and die off Unconstrgrowthamount (log_{10} CFU/g)	Unconstrained growth and die off is the simple product of Storage time and Growth per day, giving the amount of growth (log_{10} CFU/g) over the whole storage time, were growth not constrained in any way.
Chance node	Storage_time * Growthdaily
Growth per day Growthdaily (log_{10} CFU/g/day) Chance node	Growth per day adjusts calculated growth (5°C) to Storage temperature. Convert to an EGR at some other temperature via McMeekin et al. (1993). In no growth conditions – zero growth rate or Storage temperature below minimum growth temperature – the zero growth rate remains as is. For Icebox:=Refrigerator_studies Do Using localtemperature:= Storage_temperature[Refrigerator_studies=Icebox] Do if localtemperature <= Minimum_growth_tempe then (if Growth_rate<=0 then Growth_rate else 0) else if Growth_rate<=0 then Growth_rate else Growth_rate * (localtemperature-Minimum_growth_tempe)^2/(5-Minimum_growth_tempe)^2

A2.2.11 Growth characteristics

Growth characteristics are the exponential *Growth rates*, the *Minimum Growth Temperature* and the *Stationary Phase Population*. The influence diagram is shown in Figure A2.9. The Growth rates node is a table of means and standard deviations for the growth rate, log_{10}/day, at 5°C, gleaned from versions of FDA/FSIS (2001). Storage temperature is explicitly accounted for as a dependent condition for growth. It is assumed that the range of growth rates (FDA/FSIS, 2001) samples among the other dependent conditions (a_W, pH, NaCl, NO_3). Values are shown in Table A2.12. Growth rate selects values according to Normal(mean, standard deviation) for this exposure assessment. FDA/FSIS (2001) provides maximum Stationary phase population values that change with temperature. Minimum growth temperature is implemented as Triangular(1°C, 1.1°C, 2°C) for this exposure assessment.

A2.2.12 Growth conditions

The *Growth conditions* module gives a summary of growth and survival. For example, it converts the *Growth rate* simulated for 5°C into a *Generation time*, via $log_{10}(2)$/Growth rate. Also, it summarizes the growth situations, by tabulating from the simulated growth, to report the fraction of cases where the conditions jointly point to growth, no growth and die-off of the population. Nodes on the left-hand side of the diagram (Figure A2.10) are defined elsewhere, but are displayed here for continuity. Storage temperature and Storage time are defined in the Storage conditions module. Growth rate and Minimum growth temperature are defined in the Growth characteristics module. Growth per day is defined in the Growth module.Details of the notes are presented in Table A2.13.

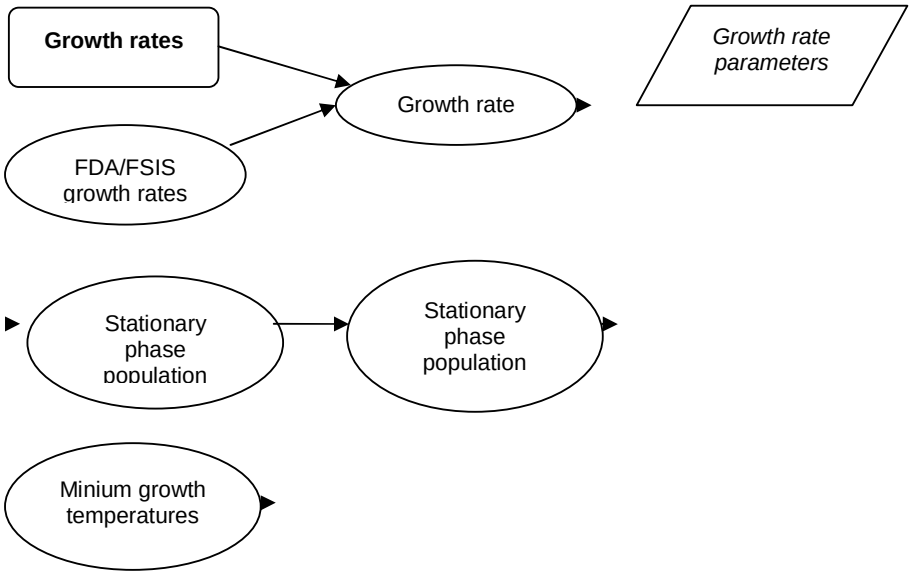

Figure A2.9 Influence diagram for *Growth characteristics* module.

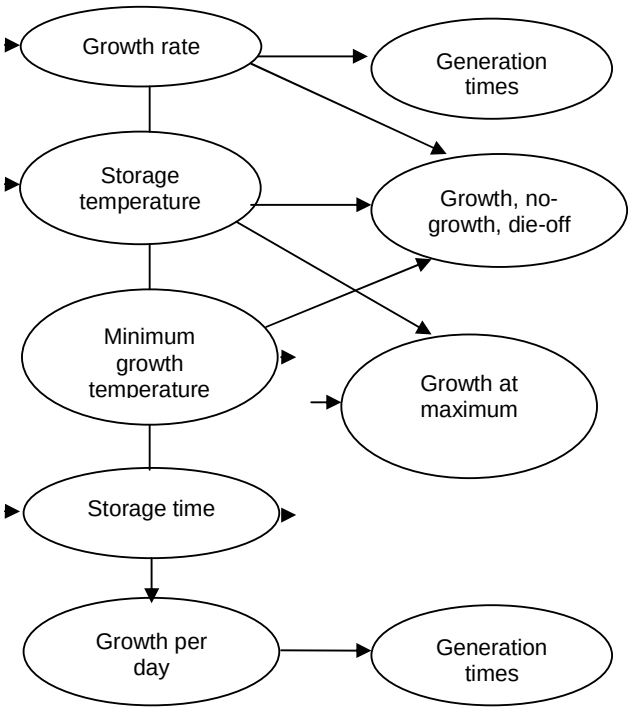

Figure A2.10 Influence diagram for *Growth conditions* module.

Table A2.12 Nodes for *Growth characteristics* module.

Title, Identifier, Structure	Description and Definition
Growth rates Growth_rates Variable node	FDA/FSIS 2001 suggests these Growth rates. We summarize the growth rates by the mean and standard deviation. Other summaries of growth rates appear in such as Farber and Peterkin (2000: Table 44-10). In order by Food groups, the definition specifies the mean, variance and number of studies. Determtable(Food_groups,Growthtableparameter)(0,Uniform(0.092, 0.434))
FDA/FSIS growth rates Fda_fsis_growth_rate Chance node	FDA/FSIS growth rates Determtable(Food_groups) (0,Uniform(0.092, 0.434))
Stationary phase population intermediate Stationary_phase_int Chance node	Stationary phase population intermediate is modelled as different for milks and for other foods of interest. Also, it varies with a range of Storage temperature. Using Allotherfoods:=(if Storage_temperature<5 then 10^5 else if Storage_temperature>7 then 10^8 else 10^6.5) Do Using Milks:=(if Storage_temperature<5 then 10^7 else if Storage_temperature>7 then 10^8 else 10^7.5) Do Table(Food_groups) (Allotherfoods, Allotherfoods, Milks, Milks, Allotherfoods, Allotherfoods, Allotherfoods)
Minimum growth temperature Minimum_growth_tempe Chance node	Farber and Peterkin (2000: Table 44-9) and its references suggest Minimum growth temperature between 1°C and 2°C for foods. The structure of the definition leaves room for the Minimum growth temperature to be different for each Food group, but leaves it the same, regardless of the set of Growth rates. Determtable(Food_groups,Updates)(Triangular(1, 1.1, 2), -1.18, Triangular(1, 1.1, 2), -1.18)
Growth rate Growth_rate Chance node	Though indexed by Updates (WHO/FAO 2000.06.17, FDA/FSIS 2000.05.19), Growth rate uses the FDA/FSIS growth rates for both. Growth rate has the simulated distribution of growth rate, for the food of interest, at 5°C. Table(Updates) (Fda_fsis_growth_rate, Fda_fsis_growth_rate)
Stationary phase population Maximum_population Chance node	Stationary phase population selects only the maximum density from Stationary phase population intermediate, for the selected Food groups. Stationary_phase_int[Food_groups=Food_groups]
Growth table parameters Growthtableparameter Index node	Growth table parameters structures the Growth rates table. ['mean', 'std. dev.', '# studies']