Joint FDA / Health Canada Quantitative Assessment of the Risk of Listeriosis from Soft-Ripened Cheese Consumption in the United States and Canada: Interpretive Summary

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BACKGROUND

In the United States and Canada, sporadic cases and some outbreaks caused by the bacterium *Listeria monocytogenes* have been strongly associated with cheese, particularly soft and soft-ripened cheese. As part of an ongoing evaluation of the safety of soft-ripened cheese, the U.S. Department of Health and Human Services / Food and Drug Administration (FDA) and Health Canada - Santé Canada (HC-SC) / Food Directorate have conducted an assessment of the risk posed by *L. monocytogenes* in these products. The assessment provides estimates of that risk and of the effectiveness of measures to reduce it, including the use of pasteurized milk. The results provide risk managers with science-based information to use in making decisions about food policies meant to protect the public from foodborne illness.

L. monocytogenes is a bacterium that is common in the environment and can be found in agricultural and food-processing settings, where it tends to persist once established. It might affect only the gastrointestinal tract, but may invade other parts of the body, potentially causing septicemia, meningitis, encephalitis, spontaneous abortion, and stillbirth. Listeriosis is not among the most commonly reported foodborne illnesses and may be mild in otherwise healthy people, but it can be very serious, particularly among susceptible populations.[1] Invasive listeriosis (cases in which the bacteria spread beyond the gastrointestinal tract) is among the leading causes of death from foodborne illness in the U.S and Canada. The elderly, pregnant women, and people with pre-existing conditions that weaken the immune system are the most susceptible.

Risk managers charged the scientists who conducted this risk assessment with:

- evaluating the effect of factors, such as presence and amounts of *L. monocytogenes* in milk, the impact of contamination or manufacturing practices at specific cheese-manufacturing steps, and conditions during distribution and storage, on the overall risk to the consumer; and
- evaluating the effectiveness of various changes in manufacturing processes and intervention strategies on reducing human illness.

This risk assessment estimates the effectiveness of various mitigations, but does not evaluate factors that may influence the choice to apply those mitigations, such as cost, feasibility, or availability. The risk managers who will use the results of this risk assessment to inform their food-safety decisions might opt to incorporate those kinds of factors, depending on their varying needs and situations.

A draft interpretive summary, draft report, draft appendices, and the draft Analytica® model were made available, on February 8, 2013, for public comments (Federal Register, Vol. 78, No. 28, pp 9701-9702). The comment period closed April 29, 2013. We received 96 comments. We considered the comments that pertained directly to the risk assessment and have responded to

[1] See the risk assessment report for references.

them in a separate document.[2] Some of the revisions to the draft of the full risk assessment report were made in response to these comments.

This document summarizes the risk assessment's key results. Its *Summary of Key Risk Results* section is written for readers from any area of expertise, including non-scientific disciplines. The *Technical Notes* section highlights some aspects of how the risk assessment was done, considers some details that do not appear in the *Summary of Key Risk Results*, and discusses data gaps and research needs revealed while developing this risk assessment. The full risk assessment report, the appendices, the answers to the public comments, and the Analytica® model are available separately at http://www.fda.gov/Food/FoodScienceResearch/RiskSafetyAssessment/.

Table 1: General information

Pathogen	*Listeria monocytogenes*
Food	Soft-ripened cheese
Populations	General populations of U.S. and Canada, including at-risk subpopulations (pregnant, immunocompromised, elderly)
Endpoint	Invasive listeriosis
Risk expression	Probability of invasive listeriosis per serving of soft-ripened cheese

SUMMARY OF KEY RISK RESULTS

To conduct the risk assessment, scientists created mathematical models and used them to predict (1) the risk from *L. monocytogenes* in soft-ripened cheese and (2) the impact of various measures meant to reduce the risk. For example, they established baseline estimates for risk from *L. monocytogenes* in soft-ripened cheese made from pasteurized-milk and in soft-ripened cheese made from raw-milk. The scientists then compared the changes in those estimates if specific measures for reducing contamination were applied.

Risk: basic results

Table 2 reports the predicted number of servings per case of invasive listeriosis, by subpopulation, in each country. It also contrasts the risk from soft-ripened cheese made with pasteurized milk and the risk from soft-ripened cheese made from raw-milk, for each subpopulation. The risk from soft-ripened cheese made from raw-milk is higher, as shown in Table 2, compared with soft-ripened cheese made from pasteurized-milk. This difference in risk is a reflection of:

- the higher rate of *L. monocytogenes* contamination in servings of soft-ripened cheese made from raw-milk (as shown in Table 3); and

[2] Joint FDA / Health Canada Quantitative Assessment of the Risk of Listeriosis from Soft-Ripened Cheese Consumption in the United States and Canada: Replies to Public Comments available at http://www.fda.gov/Food/FoodScienceResearch/RiskSafetyAssessment/

- the higher number of *L. monocytogenes* bacteria in contaminated servings of soft-ripened cheese made from raw-milk.

The net result is approximately, a 50- to 160-fold increase in the risk of listeriosis from a serving of soft-ripened cheese made from raw-milk, compared with soft-ripened cheese made from pasteurized milk (see Table 4). Although the absolute risk for the general population is lower than the absolute risk for the immunocompromised population, the relative changes in risk for the two populations are comparable.

The predicted number of *L. monocytogenes* in contaminated servings at the time of consumption varies greatly. Most contaminated servings have very few bacteria, but a few have a high load, especially contaminated servings of soft-ripened cheese made from raw-milk. Among the Canadian elderly population at baseline, for example, 50% of contaminated servings of soft-ripened cheese made from pasteurized-milk are predicted to have four or fewer colony-forming units (cfu, a count of the number of viable bacterial cells) per serving, and 90% are predicted to have fewer than 760 cfu. In comparison, 50% of contaminated servings of soft-ripened cheese made from raw-milk are predicted to have 2,200 or more cfu, and 10% are predicted to have more than 2,000,000 cfu.

Although the risk from soft-ripened cheese made from raw-milk is higher, the results show that soft-ripened cheese made from pasteurized-milk also carries some risk. The main factor that influences risk per serving of soft-ripened cheese made from pasteurized-milk is the amount of *L. monocytogenes* growth in soft-ripened cheese, particularly while the consumer stores this cheese at home. *L. monocytogenes* is a bacterium that can grow at refrigerator temperatures, given the right conditions.

Table 2: Predicted number of servings resulting in one case of invasive listeriosis.

Population	Canada	Canada	United States	United States
type of milk used	***Pasteurized***	***Raw***	***Pasteurized***	***Raw***
Elderly	138 million	2.6 million	136 million	1.2 million
Pregnant	56 million	1.1 million	55 million	570,000
Immunocompromised	163 million	2.4 million	193 million	1.2 million
General population	7,290 million	105 million	8,644 million	55 million

Table 3: Predicted prevalence of contaminated servings.

Cheese	Canada	United States
Soft-ripened cheese made from pasteurized-milk	**0.6%** (*i.e.*, 6 contaminated per 1,000 servings)	**0.7%**
Soft-ripened cheese made from raw-milk	**3.2%**	**4.7%**

Table 4: Predicted X-fold increased risk of invasive listeriosis, per serving, if raw-milk (*vs*. pasteurized) used in soft-ripened cheese.

Population	Canada	United States
Elderly	**53**-fold higher risk	**112**-fold higher risk
Pregnant	**52**	**96**
Immunocompromised	**69**	**157**
General population	**69**	**157**

Risk: effects of interventions

Among the intervention options evaluated for soft-ripened cheese made from raw-milk, two interventions led to a mean risk lower than the one obtained in the soft-ripened cheese made from pasteurized-milk baseline case:

- testing every lot of soft-ripened cheese made from raw-milk and removing positive lots from the supply chain. However, among the scenarios we evaluated, the risk reduction from this intervention is not achieved if only some lots, rather than all lots, are tested;
- applying a procedure that reduces the bacterial load by 1,000,000-fold (6 $\log_{10}$) in milk.

Other options that were considered for soft-ripened cheese made from raw-milk were found to be less effective than testing all soft-ripened cheese lots or applying a 6 $\log_{10}$ reduction:

- Excepting soft-ripened raw-milk cheese from U.S. and Canadian regulations that require such cheese to age a minimum of 60 days at 2°C (35°F) or more (Canada: Food and Drugs Act B.08.030, B.08.043, B.08.044 and U.S.: 21 CFR 133.182(a)). Reducing the aging time for soft-ripened raw-milk cheese would reduce the amount of time available for *L. monocytogenes* to grow in the soft-ripened cheese before it is eaten. This would reduce the risk of invasive listeriosis from eating raw-milk soft-ripened cheese approximately 1.5-fold to 1.8-fold, compared with the baseline estimate for raw-milk soft-ripened cheese. This would correspond to a 36-fold to 62-fold higher risk than the baseline risk estimate for soft-ripened cheese made from pasteurized-milk. This risk assessment does not consider the effect of removing the regulation on the risk of illness from other pathogens that may be present in soft-ripened cheese made from raw-milk;
- A mild treatment that kills 99.9% of the bacteria (3 $\log_{10}$ reduction) in bulk raw milk before cheese-making, including pathogens, would reduce the mean risk approximately 7.2-fold to 10-fold, compared with the baseline estimate for soft-ripened cheese made from raw-milk. This would correspond to a 7.4-fold to 11-fold higher risk than the baseline risk estimate for soft-ripened cheese made from pasteurized-milk. Treatments that kill 99.99% or 99.999% of the bacteria (4 $\log_{10}$ reduction, and 5 $\log_{10}$ reduction, respectively) in bulk raw milk before cheese-making would reduce the mean risk approximately 35-fold to 50-fold, or 56-fold to 95-fold, respectively, compared with the baseline estimate for soft-ripened cheese made from raw-milk. This would correspond to a 1.7-fold to 2.0-fold, or 1.1-fold to 1.2-fold, higher risk than the baseline risk estimate for soft-ripened cheese made from pasteurized-milk, respectively;

- Applying a substance to the surface of soft-ripened cheese made from raw-milk that reduces the surface contamination by 100-fold (2 $\log_{10}$ reduction) would reduce the mean risk approximately 1.2-fold compared with the baseline estimate for soft-ripened cheese made from raw-milk, but the risk would still be 50-fold to 86-fold higher than the baseline risk estimate for soft-ripened cheese made from pasteurized-milk;

- Testing the bulk milk used to make soft-ripened cheese from raw-milk reduces the risk approximately 24-fold to 37-fold, but is less effective than testing lots of soft-ripened cheese made from raw-milk, and still results in higher risk than the baseline risk estimate for soft-ripened cheese made from pasteurized-milk. However, the risk would still be 2.2-fold to 3.0-fold higher than the baseline risk estimate for soft-ripened cheese made from pasteurized-milk.

Table 5, below, summarizes and compares the changes in risk estimates relative to the baseline risk estimate for soft-ripened cheese made from pasteurized milk, if specific measures meant to reduce the risk are applied.

Table 5: Impact of interventions on mean risk of invasive listeriosis, per soft-ripened cheese serving (elderly population, Canada and U.S.).*

Intervention	Relative to baseline of pasteurized-milk soft-ripened cheese Canada	Relative to baseline of pasteurized-milk soft-ripened cheese United States
Soft-ripened cheese made from pasteurized-milk, at baseline	**1 (Reference)**	**1 (Reference)**
Soft-ripened cheese made from raw-milk, at baseline (*i.e.*, aged 60 days before sale)	**53**	**112**
The values above indicate that, at baseline, soft-ripened cheese made from raw-milk was predicted to be 53 times riskier than soft-ripened cheese made from pasteurized-milk, in Canada, and 112 times riskier in the U.S., with respect to invasive listeriosis.	-	-
The values below indicate that, although the interventions reduce the predicted risk of invasive listeriosis from soft-ripened cheese made from raw-milk, only the last two shown resulted in a lower predicted risk of invasive listeriosis than did using pasteurized milk to make cheese.	-	-
Soft-ripened cheese made from raw-milk, if the 60-day aging regulation is removed	**36**	**62**
Soft-ripened cheese made from raw-milk, if substance that reduces surface contamination by 2 $\log_{10}$ is applied	**50**	**86**
Soft-ripened cheese made from raw-milk, if milk is tested in farm bulk tank and removed if tests are positive**	**2.2**	**3.0**
Soft-ripened cheese made from raw-milk, if process is applied that leads to 3 $\log_{10}$ reduction of *L. monocytogenes* contamination in incoming milk	**7.4**	**11**
Soft-ripened cheese made from raw-milk, if process is applied that leads to 4 $\log_{10}$ reduction of *L. monocytogenes* contamination in incoming milk	**1.7**	**2.0**
Soft-ripened cheese made from raw-milk, if process is applied that leads to 5 $\log_{10}$ reduction of *L. monocytogenes* contamination in incoming milk	**1.1**	**1.2**
Soft-ripened cheese made from raw-milk, if process is applied that leads to 6 $\log_{10}$ reduction of *L. monocytogenes* contamination in incoming milk	**0.84**	**0.80**
Soft-ripened cheese made from raw-milk, if all cheese lots are tested and lots with positive samples are removed**	**0.08**	**0.13**

** Details and limitations available in full report.*

*** Volume tested: 50 ml for milk, 50 g made of 10 g from each of five cheeses at random for cheese lot; single* L. monocytogenes *detection probability: 0.75; test frequency: 100% of farm milk production and cheese lots.*

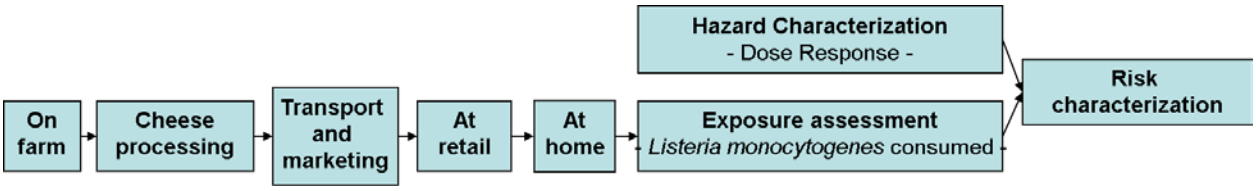
TECHNICAL NOTES

This section is a general description of the methods used for the risk assessment. In it, we make only general comments about the risk assessment and how the risk estimates reported in the *Summary of Key Risk Results* were constructed. Here, the description is less technical than in the full risk assessment report, but follows some of the same structure – hazard identification, hazard characterization, exposure assessment, and risk characterization – that the full report does.

General

None of the risk results can be observed directly, measured directly, or extracted from the microbiological literature. Indeed, some of the risk interventions that the FDA and HC-SC management charge set as objectives for the project either are not in place or are not in practice at this time. The risk results of interest can be synthesized using mathematical models, sometimes described as *process pathway* models, diagramed as in the picture below (Figure 1). The model structure is based on information from the literature, on previous risk assessments, and on consultation with experts.

Figure 1: Schematic view of the product pathway and risk assessment.



Data for the process pathway model came from the animal husbandry and microbiological literature, government nutrition surveys, home storage time and temperature surveys, and expert elicitations. All of the data used were reviewed and judged to be appropriate for the risk assessment. However, none of these sources provide perfect, certain information about a given part of the process pathway model. Rather, the data provide *inferences* about the model inputs or parameters of interest, but inferences with uncertainty that can be partly quantified.

This is a fully quantitative risk assessment, with quantitative risk results, conducted according to *Codex alimentarius*, U.S. and Canadian frameworks that call for separate evaluation of how much the risk estimates vary – for example, risk among different populations and subpopulations and risk according to serving size – and of how much uncertainty the estimates include.

A full risk assessment describes the nature of the hazard, the exposure pathway, and the consequences. In this summary, we include only a small amount of detail, and leave the rest to the full report and its references.

Hazard characterization, dose-response assessment

In a quantitative risk assessment focusing on foodborne illness, the hazard characterization includes a dose-response assessment that describes the fraction of a population who would become ill from consuming a particular number of cells of the target pathogen. That fraction decreases from 100% at very large numbers of the pathogen consumed to 0% when no cells are consumed, consistent with what experts hold to be the case for the pathogen.

This risk assessment uses a dose-response function for *L. monocytogenes* that another risk assessment developed from epidemiologic data on the number of listeriosis cases in the U.S. and earlier estimates of presence and levels of *L. monocytogenes* in all foods.

Exposure assessment

In a risk assessment, the exposure assessment describes how often and at what levels consumers in the population consume the hazard in the food of interest. In this risk assessment, the number of *L. monocytogenes* consumed in contaminated food on each occasion is the important output from the exposure assessment. This output is developed using information about the sources of contamination, the growth of *L. monocytogenes*, and serving sizes of soft-ripened cheese.

Sources of contamination

L. monocytogenes is a pathogen that is common in the environment and can be found in agricultural and food-processing settings, where it tends to persist once established. It has been isolated from soft-ripened cheese and it is considered that *L. monocytogenes* in soft-ripened cheese can originate either in the raw material, bulk milk used to manufacture cheese, or can come from the processing plant environment. Pasteurization kills *L. monocytogenes* quite effectively, but some other treatments can leave some viable *L. monocytogenes* in formed, soft-ripened cheeses. Ripening and maturation temperatures permit *L. monocytogenes* to grow, when other conditions (notably acidity and water content) permit, and the pathogen can grow to high levels under conditions of high-enough storage temperatures and long-enough storage times.

As a baseline model, we considered the manufacture of Camembert-like soft-ripened cheese made from pasteurized milk using a stabilized cheese process. For that, it was assumed that all bacteria present in the milk are definitively inactivated during the pasteurization step, so that any bacteria that survive and reach the consumer stage must come not from the raw milk, but from contamination after the soft-ripened cheeses are formed. Detection and enumeration data obtained on soft-ripened cheeses at retail in two U.S. states inform inferences about the frequency and amount of *L. monocytogenes* contamination.

For soft-ripened cheeses made from raw milk, the risk assessment accounts for the possibility of contamination from the raw milk from the farm, as well as potential in-plant environmental contamination. We analyzed farm bulk-tank surveys done in Canada and the U.S. to estimate the level of contamination in bulk-tank raw milk and how much it varies.

Growth

L. monocytogenes populations can increase, when conditions are right, from the point of contamination to the point of consumption. Predictive microbiology models are the primary

means to estimate the amount of growth, using inferences about growth parameters from the literature (lag times before growth begins, growth rates, and maximum achievable densities of bacteria in the product) and describe growth over the times and at the temperatures experienced in transport, distribution, and retail and home storage.

Serving sizes

Data from government nutrition surveys in Canada and the U.S. enable us to describe how much soft-ripened cheese serving sizes vary among individuals.

Risk characterization

The exposure assessment outputs describe how the number of *L. monocytogenes* per soft-ripened cheese serving varies among subpopulations and between countries; from variation in individuals' serving sizes, home-storage times, and home-storage temperatures; with variations in transport and distribution storage time and temperature; with variation in cheese processing effects; and, with differences in contamination levels in raw materials.

Those exposure assessment outputs are combined with the dose-response model to develop the risk characterization outputs, describing how the risk estimates of interest vary. Our major outputs are expressed as the risk of invasive listeriosis per serving of soft-ripened cheese at random, and we can describe the effects of the various alternatives and interventions by the ratio of the mean risk of invasive listeriosis, per serving, for the alternative scenario considered, to the mean risk of invasive listeriosis, per serving, for the baseline estimate for soft-ripened cheese made from pasteurized-milk. Some results are reported in the *Summary of Key Risk Results* section above; individual estimates for soft-ripened cheese made from pasteurized-milk and soft-ripened cheese made from raw-milk are reported in Table 2.

Supplementary results for sensitivity analyses that examine how risk estimates change with changing model inputs and the amount of uncertainty one would attribute to the results in this report's Table 2 and Table 5 are available in the full report.

Data gaps and research needs

The development of the risk assessment revealed some gaps in data. These are described in the main report and are explored in the uncertainty analysis. We concluded that no critical data gaps impair the conclusions of this risk assessment. For example, the exact processing may differ from one soft-ripened cheese to another. However, the general conclusions, *i.e.*, that the risk of listeriosis from consumption of soft-ripened cheese made from raw milk is substantially larger than that for consumption of soft-ripened cheese made from pasteurized milk, that the 60-day aging regulation actually increases the risk of listeriosis for consumption of raw-milk cheeses, that a 6 log reduction (or equivalent) of the contamination in milk is necessary to make raw-milk cheeses as safe from listeriosis as pasteurized-milk cheeses, and that most other strategies are not sufficient by themselves - apply to any soft-ripened cheese in or on which *Listeria monocytogenes* can grow substantially. Some additional data would decrease the uncertainty in the risk estimates.