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

Food Directorate / Direction des aliments
Health Canada / Santé Canada

Center for Food Safety and Applied Nutrition
Food and Drug Administration
U.S. Department of Health and Human Services

2012

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 designed to reduce it. 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. It is not among the most commonly reported foodborne illnesses and may be mild in otherwise healthy people, but listeriosis can be very serious, particularly among susceptible populations.[1] It is among the leading causes of death from foodborne illness in the U.S. 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
- making it possible to evaluate 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.

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 limitations of the risk assessment. The full risk assessment report is available separately at *http://www.fda.gov/food/scienceresearch/researchareas/riskassessmentsafetyassessment/*.

[1] See the draft risk assessment report for references.

Table 1: General information	
Pathogen	*Listeria monocytogenes*
Food	Camembert, as an example of 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 pasteurized-milk cheese and in raw-milk cheese. 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 cheese made with pasteurized milk and the risk from raw-milk cheese for each subpopulation. The risk from raw-milk cheese is higher, as shown in Table 2, compared with pasteurized-milk cheese; a reflection of:

- the higher rate of contamination in servings of raw-milk cheese (as shown in Table 3); and
- the higher number of *L. monocytogenes* bacteria in contaminated servings of raw-milk cheese.

The net result is a 50- to 160-fold increase in the risk of listeriosis from a serving of soft-ripened raw-milk cheese, compared with cheese made from pasteurized milk (see Table 4).

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 raw-milk cheese. Among the Canadian elderly population at baseline, for example, 50% of contaminated pasteurized-milk cheese servings are predicted to have four or fewer colony-forming units (cfu, number of viable bacterial cells) per serving, and 90% are predicted to have fewer than 760 cfu. In comparison, 50% of contaminated raw-milk cheese servings 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 raw-milk cheese is higher, the results show that pasteurized-milk cheese does carry some risk, as well. The main factor that influences risk per serving of pasteurized-milk cheese is the amount of *L. monocytogenes* growth in the cheese, particularly while the consumer stores the 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.				
	Canada		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
Corresponds to values for mean risk.				

Table 3: Predicted prevalence of contaminated servings.		
	Canada	United States
pasteurized-milk cheese	**0.6%** (*i.e.*, 6 contaminated per 1,000 servings)	**0.7%**
raw-milk cheese	**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.		
	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 raw-milk cheese, testing every raw-milk cheese lot and removing positive lots from the supply chain is the only alternative that leads to a mean risk lower than the one obtained in the pasteurized-milk cheese baseline case. 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.

Other options that were considered for raw-milk cheese were found to be less effective than testing cheese lots:

- Removing the regulation that requires a minimum of 60 days of aging, 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)) would reduce the amount of time available for *L. monocytogenes* to grow in soft-ripened cheese before being 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 risk assessment does not consider the effect of removing the regulation on the risk of illness from other pathogens that may be present in raw-milk soft-ripened cheese or from other types of cheese.

- 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-fold to 10-fold, compared with the baseline estimate for raw-milk cheese. This intervention is not

full milk pasteurization. Properly applied, full milk pasteurization kills *all* bacteria in raw milk.

- Testing the bulk milk used to make raw-milk cheese reduces the risk approximately 27-fold to 37-fold, but is less effective than testing raw-milk cheese lots, and still results in higher risk than the baseline risk estimate for pasteurized-milk cheese.

Table 5, below, summarizes and compares the changes in risk estimates 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.).*

	Relative to baseline of pasteurized-milk cheese	
Intervention	**Canada**	**United States**
Pasteurized-milk cheese, at baseline	**1 (Reference)**	**1 (Reference)**
Raw-milk cheese, at baseline	**53**	**112**
The values above indicate that, at baseline, raw-milk cheese was predicted to be 53 times riskier than pasteurized-milk cheese, 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 raw-milk cheese, only the last one shown resulted in a lower predicted risk of invasive listeriosis than did using pasteurized milk to make cheese.		
Raw-milk cheese, if the 60-day aging regulation is removed	**36**	**62**
Raw-milk cheese, if process is applied that leads to 3 $\log_{10}$ reduction of *L. monocytogenes* contamination in incoming milk	**7**	**11**
Raw-milk cheese, if milk is tested in farm bulk tank and removed if tests are positive**	**2**	**3**
Raw-milk cheese, if all cheese lots are tested and lots with positive samples are removed**	**0.080**	**0.134**

** Details and limitations available in full report.*
*** Volume tested: 50 ml for milk, 50 g composite 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.*

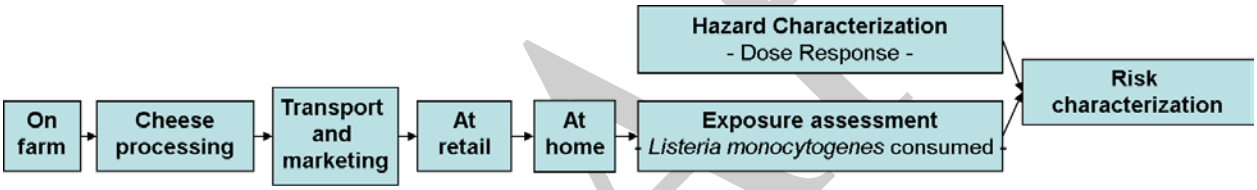
TECHNICAL NOTES

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 parts of that 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 fully 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 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 soft-ripened cheese (Camembert-like) 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 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 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 soft-ripened cheese serving 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, pasteurized-milk cheese estimate. Some results are reported in the *Summary of Key Risk Results* section above; individual estimates for pasteurized-milk cheese and raw-milk cheese 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.

LIMITATIONS

The model, results, and conclusions are limited to *L. monocytogenes* and Camembert-like cheeses. Notably, the function predicting the bacterial growth relies on the extensive growth information available for Camembert cheese, and these results do not necessarily apply to other cheeses in which *L. monocytogenes* has different growth characteristics.

The prevalence and level of contamination in Canada and in the U.S. rely on a single study to infer in-plant environmental *L. monocytogenes* contamination. Additional information about the prevalence of contaminated lots and contaminated cheeses within lots is needed.

There is considerable uncertainty in the dose-response model. Sensitivity analyses showed us that, within the small part of the overall uncertainty that is considered here, the uncertainty surrounding the dose-response function dominates any other source. Caution should be used when comparing the absolute values obtained in this risk assessment with other results obtained using a different dose-response model.

Predictive modeling was used to model the growth of *L. monocytogenes* in soft-ripened cheeses between the point of retail and the point of consumption, and the exposure assessment was based on information derived from those models. There is, notably, a lack of information on *L. monocytogenes* growth in naturally contaminated cheese, as well as a lack of information on the growth of *L. monocytogenes* in the presence of natural cheese flora (such as that present in raw-milk cheese).

As with all model-based studies, the results also rely on extrapolations; for example, over time, from bulk-tank surveys carried out in the 1990s to current farm bulk-tank characteristics, and from soft cheese consumption in the early 2000s to that in the present. Other examples include extrapolations of U.S. home storage data to those for Canada; from U.S. contamination frequency and levels at retail to those in Canada; and from laboratory scale, where most studies of pathogens in cheese have been done, to production scales, the source of most of the cheeses that we eat. Any biases and uncertainty those extrapolations may have introduced are unknown.