Appendices

Appendix 1

Chronology of Technical and Scientific Reviews of the Draft FDA/FSIS *Listeria monocytogenes* Risk Assessment Document

Appendix 1: Chronology of Technical and Scientific Reviews of the Draft FDA/FSIS *Listeria monocytogenes* Risk Assessment Document

We solicited the advice and opinions of scientific experts and the public throughout the conduct this draft *Listeria monocytogenes* risk assessment. A summary of the dates, type of review activity, and participants is provided below.

Chronology of Technical and Scientific Reviews of the FDA/FSIS *Listeria monocytogenes* Risk Assessment

Date	Activity	Participants
January 1999	Risk Assessment Team assembled	FDA and FSIS
May 7, 1999	Federal Register Notice; request for comments and for scientific data and information	Public; Federal Register Notice
May 7, 1999	Federal Register Notice of public meeting; request for comments	Public; Federal Register Notice
May 27, 1999	Public meeting (Chicago, IL)	NACMCF public
August 13, 1999	Federal Register Notice of public meeting	Public; Federal Register Notice
September 23, 1999	Public meeting; request for comments on the risk assessment approach and assumptions (Washington, DC)	NACMCF; Public
December 1999	Request for scientific review of draft risk assessment document	RAC members
December 1999	Technical discussion of the draft risk assessment document	RAC annual meeting (closed)
December 1999	Intensive review of model	FDA
March 31, 2000	Internal scientific review of draft document	Selected FDA risk managers
May 29, 2000	Technical review of document	Selected government experts and SGE's
May 29, 2000	Review of model and mathethematics	Selected government experts and SGE's
May 29, 2000	Data verification	FDA quality assurance team,
Sept. to Oct., 2000	Interagency review of draft document	FDA, FSIS, CDC
December 2000	Federal Register Notice of availability of draft risk assessment document for public review and comment	Public
Early 2001	Public meeting; presentation of assumptions, approach, and results of the risk assessment and request for comment	Public

FDA= Food and Drug Administration
FSIS= Food Safety and Inspection Service
NACMCF = the National Advisory Committee on Microbiological Criteria for Foods.
RAC = the U.S. government Interagency Risk Assessment Consortium
SGE = Special Government Employees

Appendix 2

An overview of the FDA/FSIS Risk Assessment

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Overview of the Risk Assessment

The FDA/FSIS *Listeria monocytogenes* risk assessment organizes currently available information on listeriosis. It was designed to examine broad groups of foods most likely to cause listeriosis, it does not determine whether a food category is 'safe.' We did not model the source or process of contamination of the food, but did include expected growth between retail and consumption. For frankfurters that are usually heated before consumption, the reheating step was modeled, to allow for those occasions where the food is not adequately heated to kill all microorganisms. The model provided a baseline or description of our best estimate of the role the selected foods play in the threat from listeriosis in the United States. The model did not attempt to evaluate any mitigations that might be imposed to reduce the risk from listeriosis. This could be the objective of a subsequent risk assessment. Another objective of this risk assessment was to collect information on the dose-response relationship and develop a model to estimate the likelihood of listeriosis from consuming specific numbers of *L. monocytogenes*.

This risk assessment provides an estimate of the degree of certainty associated with the data. To accomplish this, we used distributions of the data so that real differences that exist for an individual parameter would be represented instead of using point estimates or means. Contamination levels in different samples, amount consumed per servings, *L. monocytogenes* growth rates for foods within a group and lengths of storage time by the consumer are data that were considered in the model as distributions.

Although the risk assessment uses the best data available, one of the important roles of the risk assessment is to determine critical absences of adequate data that drive the uncertainty in the overall risk assessment. Thus, risk assessment can be used as a link between risk management and research. Risk managers should consider uncertainty when evaluating the significance of a parameter. In some instances, uncertainty may be too large to allow making inferences from the risk assessment. The risk assessment presents the scientific information, both what is known and the degree of certainty. The risk assessment does not impose a judgement or make value decisions based upon the information, that is the role for risk management.

The Risk Assessment Process: Flow Chart

Figures A2-1 and A2-2, below, depict the risk assessment process that is briefly described in the Introduction section of the risk assessment and fully described in subsequent sections.

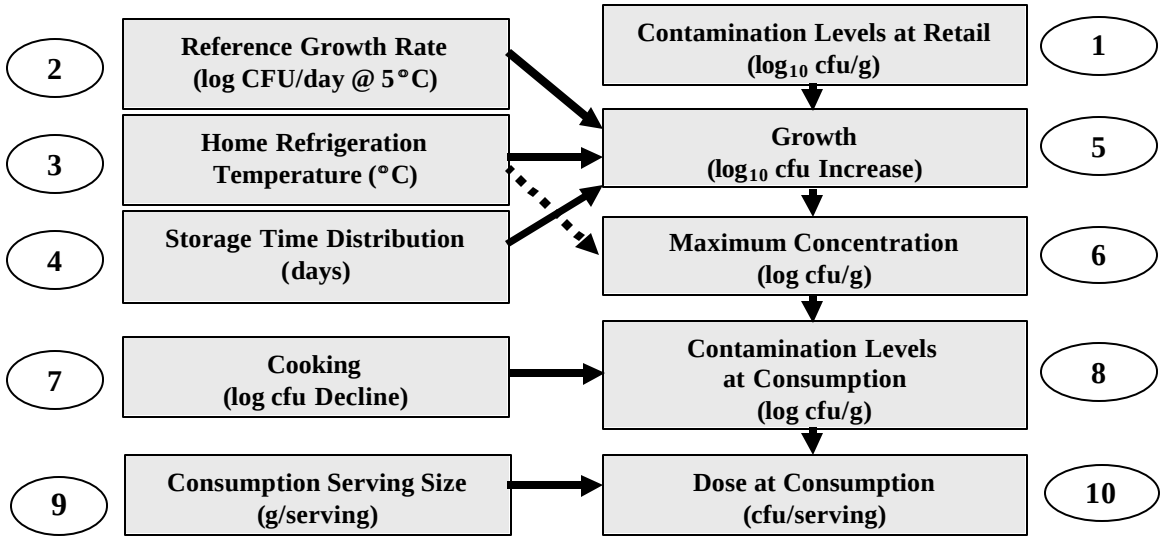

Figure A2-1. Flow chart of *L. monocytogenes* risk assessment model for individual exposure components. This part of the model was integrated with a two-dimensional simulation where one dimension characterized the variability among meals, while the second dimension characterized the uncertainty in the prediction. A different simulation was performed for each food category. Exposure assessment steps are identified in light gray boxes and the hazard characterization steps are in medium gray boxes.

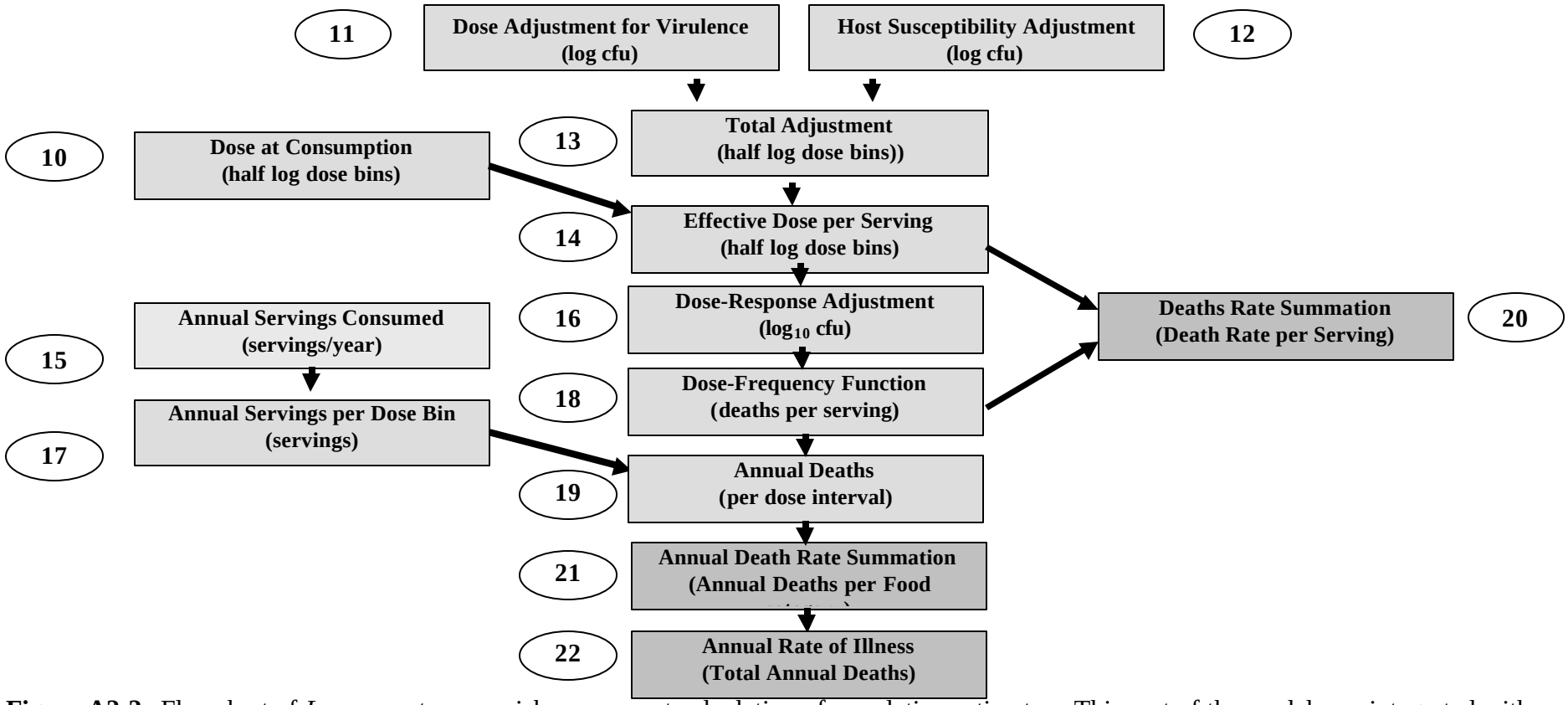

Figure A2-2. Flowchart of *L. monocytogenes* risk assessment calculation of population estimates. This part of the model was integrated with a one-dimensional Monte-Carlo, where the single dimension represents uncertainty. The subpopulations were modeled separately. Exposure assessment steps are identified in light gray boxes, the hazard characterization steps are in medium gray boxes, and the risk characterization steps are in dark gray boxes.

Description of Calculations for Each Step in the Model

Figures A2-1 and A2-2 show the order of the calculations used in the modeling for this risk assessment.

Step 1. Distributions for contamination at retail for each food category.

Step 2. Distributions for the reference growth rate at 5°C for each food category.

Step 3. A distribution of home refrigerator temperatures in the United States, this distribution was used for all food categories.

Step 4. Distributions for post-retail storage time for each food category.

Step 5. The growth model used for all food categories. The growth model was triggered only for servings with one or more bacterium. This section calculated the exponential growth rate for the refrigeration temperature and multiplied that by the storage time.

Step 6. The maximum concentration for each food category. Post growth *L. monocytogenes* concentrations were truncated at this level. The maximum growth was temperature dependent with more growth allowed at higher refrigeration temperatures.

Step 7. A model representing the effect of reheating frankfurters on *L. monocytogenes* concentration, used for frankfurters only.

Step 8. Net contamination at time of consumption. Calculated with inputs from steps 1, 6, and 7.

Step 9. Distributions of serving size for each food category.

Step 10. Distributions of dose at consumption for each food category. This is the final output of the 2D simulation. After collapsing the variability dimension to half-log dose bins, the output for each food category was conveyed to the 1D dose-response simulation for each population group.

Step 11. A distribution for variability of *L. monocytogenes* strain virulences in mice, with the implicit assumption that a similar range will be observed in humans.

Step 12. A distribution adjusting for variability in host susceptibility among humans, with three (High, Medium, Low) separate adjustments applied to represent different possible ranges. The adjustment increased the range of effective doses.

Step 13. The sum of the strain variability (step 11) and host susceptibility distributions (step 12) obtained by 2D Monte-Carlo, with 100,000 variability iterations and 300

uncertainty iterations. The variability dimension was then collapsed to half log dose bins.

Step 14. Summation of the exposure assessment (step 10) and adjustment factor (step 13) for each food category

Step 15. The annual number of meals consumed for each food category.

Step 16. Addition of the dose-response adjustment factor that is applied in order to make the predictions consistent with CDC estimates of the annual death rate attributable to the population group (i.e., the median value in step 22).

Step 17. An intermediate calculation of the number of annual servings falling in each dose bin for each food category. This was obtained by multiplying the number of servings (step 15) by the fraction falling in each effective dose bin (step 14).

Step 18. Calculation of the death rate per serving for each dose bin (from step 14), using the dose-response function derived from mouse data.

Step 19. An intermediate calculation of the number of annual deaths for each dose bin and food category. This was obtained by multiplying the death rate per serving (step 18) by the number of servings for the dose bin (step 17).

Step 20. Calculation of the death rate per serving for each food category by summing across dose bins. This was obtained by summing the product of the death rate (step 18) and serving fraction (step 14) across all bins.

Step 21. Calculation of the annual number of deaths for each food category by summing across dose bins (step 19).

Step 22. Calculation of the total number of deaths by summing across food categories

A framework that separates the assessment activities into four components; hazard identification, exposure assessment, dose-response assessment (hazard characterization), and risk characterization. This framework allows organization of a highly complex array of varied data, characterization of the predicted consequences, definition of uncertainties, and identification of data gaps.

Hazard Identification

Hazard Identification is one interface between risk assessment and risk management where the problems that the assessment is intended to address are identified and specific questions about model design are resolved. Endpoints in this assessment include death and serious illness for the intermediate-age subpopulation and two readily identifiable vulnerable subpopulations: perinates (fetuses and newborns) and the elderly (60 years of age and older).

Exposure Assessment

Exposure related to foodborne *L. monocytogenes* consumption can be separated into two main subcategories: pathways of contamination and frequency of consumption of contaminated foods. This risk assessment did not consider the pathway of contamination. With the exception of limited modeling of growth and thermal destruction during home cooking of frankfurters, this risk assessment did not take into account the effects of interventions or controls. The exposure assessment emphasized modeling foods that have a potential for *L. monocytogenes* contamination at retail.

The development of the exposure assessment included:

- Identification of foods that are known to have been associated with *L. monocytogenes* from outbreaks, sporadic cases, and national and international recalls and other sources.

- Food categories, grouped according to primary origin, epidemiological and surveillance experience, processing operations and food characteristics, and the availability of consumption and contamination data or useable proxy data.
- Development of distributions of the amount consumed per serving for each food category and estimates of the annual number of servings in U.S. using national food consumption surveys and other food consumption and census information.
- Calculation of distributions of contamination levels at retail for each food category, based on published studies of naturally-occurring *L. monocytogenes* contamination. For contamination data of foods after manufacture, growth to the retail store was estimated.
- Modeling of data to describe the opportunity for growth, decline, or inactivation of *L. monocytogenes* between the time that a food was purchased and the time it was consumed.
- Development of a mathematical model to represent inadequate reheating of frankfurters in the home. Normally a cooking or reheating step will kill microorganisms.
- Derivation of distributions of contamination levels at consumption for each food category, based on initial *L. monocytogenes* contamination, growth potential, storage duration, refrigeration temperatures and reheating.
- Derivation of estimates of the frequencies and levels of contamination of a serving, by combining distributions of food consumption frequency and amount with distributions of food contamination frequency and levels.
- Because of a lack of data, foods prepared outside the home were not modeled separately. The food consumption survey data included all eating occasions within and outside the home. It was therefore assumed that contamination at retail, refrigeration temperature, and storage times included the meals served or prepared outside of the home (restaurant and food service meals).

Hazard Characterization

For *L. monocytogenes*, the overall incidence of severe illness, and predicted relative risk to age-related susceptible subpopulations are well characterized. The relation between the amount of *L.*

monocytogenes consumed (dose) and the likelihood or severity of resultant illness from that dose (response) is not well understood. The dose-response effect is a complex function of the number of pathogens consumed, their level of expressed virulence, the food matrix that the pathogen is in, and the susceptibility and immunity of the human host.

For this *L. monocytogenes* risk assessment the following information was considered:

- Accumulating epidemiological information indicates that different strains of *L. monocytogenes* vary in their ability to cause illness. Data were utilized from animal studies that compare the virulence of *L. monocytogenes* strains isolated from humans and from foods, in order to describe the distribution of virulence among strains encountered in foods.
- Immunological and physiological factors in humans determine the distribution of susceptibility that may be found throughout a population.
- Food matrix effects have been theorized to affect the ability of a pathogen to survive inside the body (*e.g.*, the fat content of foods appears to affect the infectious dose of *Salmonella* sp.). Quantitative data specifically related to *L. monocytogenes* in humans were not available.
- Epidemiological data with the number of deaths in each population per year and the ratio of serious illness/deaths.

The probability of illness in three different subpopulations of consumers is described; perinatal (with exposure occurring *in utero* from foodborne infection of the mother during pregnancy); elderly (60 years of age and older); and intermediate-age subpopulation, which includes both healthy and immunocompromised individuals (but excludes the other two subpopulations). A host susceptibility adjustment was applied to each of the three subpopulation curves. The adjustments used animal data to establish a susceptibility range and human epidemiological surveillance data to adjust for increased susceptibility of these subpopulations.

Risk Characterization

Risk characterization integrates the distributions generated in the exposure assessment and the hazard characterization. The published literature provides an estimate of the number of illnesses and deaths attributed to *L. monocytogenes*. Therefore, the primary component of this risk characterization is a probabilistic estimate of the likelihood of illness from consumption of contaminated food from each of the 20 food categories.

The risk characterization section of this risk assessment provides the results of the assessment, and the associated uncertainty around those results. Additionally, data gaps, which, if filled, would contribute to reducing the uncertainty in the assessment, are identified to highlight critical needs for additional research.

Characteristics of Calculations Used in Risk Assessment

Monte-Carlo simulations are an integral part of most quantitative risk assessments. They include repetitive calculations with minor variations and are made possible by the development of the computer.

A large portion of this risk assessment model employs a two-dimensional Monte-Carlo simulation. One dimension represents variations associated with the capacity of individual servings of food to cause listeriosis. Sources of variation modeled include *L. monocytogenes* concentration at the retail level, amount consumed per serving, microbial growth rates, product storage times and temperatures, strain virulence, and host susceptibility. The second dimension represents the uncertainty in the predictions made.

Later portions of the risk assessment employ a one-dimensional Monte-Carlo simulation, where the range of predicted values represent uncertainty only. In this part of the assessment, the U.S. population is modeled as a whole, beginning with the estimate of the fraction of servings falling in particular dose ranges from the first part of the risk assessment.

The conclusions of the FDA/FSIS *L. monocytogenes* risk assessment are based on stochastic calculations. Thus the parameters modeled by this risk assessment are represented by distributions of values. These distributions represent both the known variation and the uncertainty in that parameter. As a result, instead of using deterministic calculations (adding or multiplying single values, usually means), this risk assessment uses simulation modeling techniques, frequently termed Monte Carlo modeling, to make its calculations. In this technique, the model is repeatedly calculated and in each iteration the process picks a new value from each of the distributions. This means that there is not a single answer to the calculation; instead, a distribution of calculated values is generated. This distribution may be graphically plotted, or it may be characterized by a distribution equation (e.g., exponential, normal) and parameter values for that equation (e.g., mean, standard deviation).

Mathematical calculations with distributions do not always form simple symmetrical normal distributions. Many distributions are asymmetrically skewed with long tails on one side. When any two distributions are added together, both the means and the variances are added. The summed distribution has a larger variance than either original distribution, and may not be of the same shape as either of the original distributions. When two normal distributions are multiplied, a Lognormal distribution results. This distribution is skewed with a tail extending toward larger values. The magnitude of the variance for the product of two distributions is much larger than the variances of the original distributions. The practical effect of this is that multi-step calculations have increasingly wider output distributions. This occurs whether the distribution includes variation, uncertainty, or both.

A skewed distribution does not have the same value for the mean and the median (half of the values above and half are below that value) as does the normal distribution. In extremely skewed distributions, the median is frequently considered a better parameter than the mean to represent the distribution, because it is not as affected by extreme values as the mean. However, summing the median values for two or more distributions does not equal the median of the summed distributions.

Appendix 3
The Foodborne Diseases Active Surveillance Network

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The Foodborne Diseases Active Surveillance Network (FoodNet) is a collaborative project of the CDC, nine Emerging Infections Program sites (California, Colorado, Connecticut, Georgia, New York, Maryland, Minnesota, Oregon and Tennessee), the Food Safety and inspection Service (FSIS), and the Food and Drug Administration (FDA). The project consists of active surveillance for foodborne diseases and related epidemiological studies designed to help public health officials better understand the epidemiology of foodborne diseases in the United States.

Foodborne diseases include infections caused by bacteria such as *Salmonella, Shigella, Campylobacter*, *Escherichia coli* O157, *Listeria monocytogenes, Yersinia enterocolitica,* and *Vibrio,* and parasites such as *Cryptosporidium* and *Cyclospora*. In 1995, FoodNet surveillance began in five locations: California, Connecticut, Georgia, Minnesota and Oregon. Each year the surveillance area, or catchment, has expanded, with the inclusion of additional counties or additional sites (New York and Maryland in 1998, Tennessee in 2000 and Colorado in 2001). The total population of the current catchment is 25.4 million persons, or 10% of the United States population.

FoodNet provides a network for responding to new and emerging foodborne diseases of national importance, monitoring the burden of foodborne diseases, and identifying the sources of specific foodborne diseases.

The mission of FoodNet is to contribute to the prevention of illness, disability, and death due to foodborne and diarrheal diseases by providing high-quality surveillance data. These data help determine the burden of foodborne diseases, monitor changes in the incidence of specific foodborne diseases in the United States, determine the proportion of specific foodborne diseases attributable to specific foods, and contribute to a network designed to respond rapidly to emerging foodborne diseases. FoodNet accomplishes its mission through active surveillance of laboratory-confirmed cases, laboratory studies, epidemiologic studies focused on specific infections, other epidemiologic studies, and investigations of outbreaks of foodborne diseases.

Appendix 4
Selected References for Food Category Identification

Appendix 4: Selected References for Food Category Identification

OUTBREAKS

CDC, 1998b, 1999b
Dalton *et al.*, 1997
Farber and Peterkin, 1991
Fleming *et al.*, 1985
Headrick *et al., 1998*
Heisick *et al.*, 1989
Ho *et al.*, 1986
Linnan *et al.*, 1988
Riedo *et al.*, 1994
Ryser, 1999a
Schlech, 1996
Slutsker and Schuchat, 1999
Schuchat *et al.*, 1991
Schwartz *et al.*, 1989
Simpson, 1996

SPORADIC CASES

Anderson *et al*., 1992
Farber and Peterkin, 1991
Mascola *et al.*, 1988, 1992
Pinner *et al.*, 1992
Slutsker and Schuchat, 1999
Schuchat *et al.*, 1991
Schuchat *et al., 1*992
Schwartz *et al.*, 1988
Tappero *et al.*, 1995

REGULATORY RECALLS by the United States (U.S.) Food and Drug Administration (FDA), U.S. Department of Agriculture/Food Safety and Inspection Service (FSIS) and the Canadian government

Farber and Peterkin, 1991 and 1999
Gravani, 1999
Jinneman *et al*., 1999
Ryser, 1999a, 1999b, and 1999c

SELECTED LITERATURE related to prevalence and incidence *of L. monocytogenes* through analytical testing in North America (the United States and Canada)

Berrang *et al.*, 1989
Beuchat and Brackett, 1990a, 1990b
Beuchat and Brackett, 1991
Beuchat and Ryu, 1997
Boerlin *et al.*, 1997
Datta *et al.*, 1988
Dillon and Patel, 1992
Dillon *et al.*, 1992
Dillon *et al.*, 1994
Farber *et al.*, 1987
Farber *et al.*, 1988
Farber, 1991a
Farber, 1991b
Farber, 1997
Farber and Peterkin, 1991
Farber *et al.*, 1998a, 1998b
Genigeorgis *et al.*, 1991
Glass *et al.*, 1998
Hayes *et al.*, 1991
Hayes *et al.*, 1992
Heinitz and Johnson, 1998
Heisick *et al.*, 1989
Johnson, 1990a
Johnson, 1990b
Johnson, 1990c
Johnson *et al.*, 1988
Kozak *et al.*, 1996
Lin *et al.*, 1996
Motes, 1991
Odumeru *et al.*, 1997
Pearson and Marth, 1990
Petran *et al.*, 1988
Piyasena *et al.*, 1998
Rawles *et al.*, 1995
Shelef, 1989a, 1989b
Steinbruegge *et al.*, 1988
Sado *et al.*, 1998
Ryser, 1999b
Weagant *et al.*, 1988

SELECTED LITERATURE (outbreaks, sporadic cases, and prevalence and incidence studies of *L. monocytogenes*) in other countries around the world.

Belgium	
	Art and Andre, 1991
	Gilot *et al*., 1997
Brazil	
	Delgado da Silva *et al*., 1998
Denmark	
	Ben Embarek, 1994
	Jensen *et al*., 1994
	Jorgensen and Huss, 1998
England and Wales	
	Fenlon *et al*., 1996
	Gilbert *et al*., 1993
	Greenwood *et al*., 1991
	Houang and Hurley, 1991
	McLauchlin *et al*., 1990
	McLauchlin *et al*., 1991
	McLauchlin, 1996
	Morris and Ribeiro, 1991
	Newton *et al*., 1992
	Nichols *et al*., 1998
	Sizmur and Walker, 1988
	Velani and Roberts, 1991
France	
	Bemrah *et al*., 1998
	Nguyen-the and Carlin, 1994
	Goulet *et al*., 1995
	Goulet *et al*., 1998
	Jacquet *et al*., 1995
	Salvat *et al*., 1995
	Swardson, 1999
Germany	
	Teufel and Bendzulla, 1993;
Greece	
	Sergelidis *et al*., 1997
Iceland	
	Hartemink and Georgsson, 1991
	Valdimarsson *et al*., 1998
India	
	Jeyasekaran *et al*., 1996
Italy	
	Cantoni *et al*., 1989
	Massa *et al*., 1990
	Pinto and Reali, 1996
	Salamina *et al*., 1996
Japan	
	Iida *et al*., 1998
	Ryu *et al*., 1992
Maylasia	
	Arumugaswamy *et al*., 1994
Mexico	
	Luisjuan-Morales *et al*., 1995
	Saltijeral *et al*., 1998, 1999

New Zealand	
	Brett *et al*., 1998
	Lennon *et al*., 1984
Northern Ireland	
	George and Levett, 1990
	Harvey and Gilmour, 1992 and 1993
	Wilson, 1995
	Wilson, 1996
Norway	
	Rorvik *et al*., 1995
	Rorvik *et al*., 1997
Spain	
	de Simon and Ferrer, 1998
	Margolles *et al*., 1996
Sweden	
	Ericsson *et al*., 1997
	Longcarevic *et al*., 1995
	Longcarevic *et al*., 1996
	Longcarevic *et al*., 1998
Switzerland	
	Bula *et al*., 1995
	Jemmi and Keusch, 1992
	Trussel, 1989
Taiwan	
	Wong *et al*., 1990
Turkey	
	Ahrabi *et al*., 1997