

US EPA ARCHIVE DOCUMENT

**Dose-Response for
*Listeria monocytogenes***

Heejeong Latimer, Ph.D.

Food Safety and Inspection Service
United States Department of Agriculture
Washington, DC 20250-3700

Better information. Better decisions. Risk assessment.

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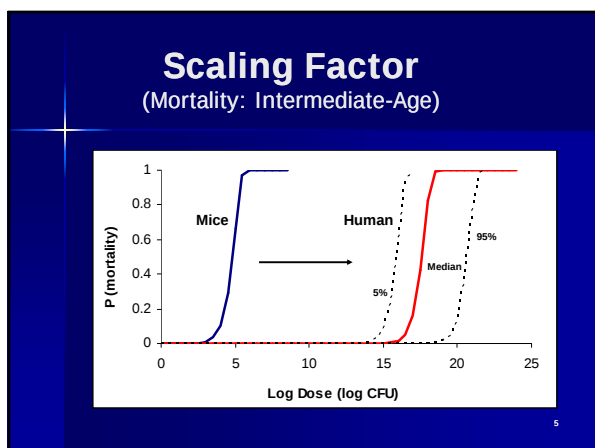
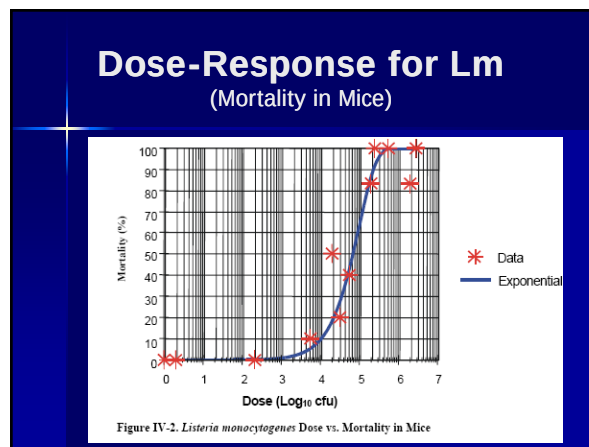
- FDA/FSIS dose-response model
- FAO/WHO dose-response model
- Other model
- Summary
- Points for Discussion
- Conclusion

Better information. Better decisions. Risk assessment.

FDA/FSIS D-R for Lm

Mice (Mortality) → Scaling Factor → Human (Mortality) → Conversion Factor → Human (Illness)

Model selected: Exponential



**Uncertainty associated with
Scaling Factors
(Mice $\Rightarrow$ Human)**

Table IV-9. Model-Dependence of the *Listeria monocytogenes* Dose-Response Scaling Factor Ranges for the Three Subpopulations

Subpopulation	Dose-Response Scaling Factor (Log ₁₀ cfu)		
	Median	5 th Percentile	95 th Percentile
Intermediate-Age	12.8	11.1	15.9
Neonatal ^a	9.0	7.9	11.6
Elderly	11.4	10.1	14.3

^a An adjustment to account for total perinatal deaths (prenatal and neonatal) is described in the risk characterization section.

Estimated Mortality Rate in Human

Table IV-12. Dose-Response with Variable *Listeria monocytogenes* Strain Virulence for Three Age-Based Subpopulations

Dose (cfu/serving)	Median Mortality Rate per Serving ^a		
	Intermediate-Age	Neonatal ^b	Elderly
1	1.5×10^{-10} (1.2x10 ⁻¹⁰ , 1.9x10 ⁻¹⁰)	1.6×10^{-10} (1.2x10 ⁻¹⁰ , 4.0x10 ⁻¹⁰)	4.0×10^{-11} (6.3x10 ⁻¹² , 1.6x10 ⁻¹⁰)
10 ³	1.2×10^{-11} (5.4x10 ⁻¹² , 6.8x10 ⁻¹¹)	1.3×10^{-11} (4.3x10 ⁻¹² , 1.7x10 ⁻¹¹)	3.6×10^{-11} (2.2x10 ⁻¹¹ , 7.2x10 ⁻¹¹)
10 ⁶	1.0×10^{-10} (1.9x10 ⁻¹¹ , 3.5x10 ⁻¹⁰)	1.3×10^{-10} (1.2x10 ⁻¹⁰ , 8.6x10 ⁻¹⁰)	3.1×10^{-10} (5.7x10 ⁻¹¹ , 3.3x10 ⁻¹⁰)
10 ⁹	1.2×10^{-9} (6.0x10 ⁻¹¹ , 1.9x10 ⁻⁹)	1.4×10^{-9} (1.6x10 ⁻⁹ , 5.1x10 ⁻⁹)	3.4×10^{-9} (1.3x10 ⁻⁹ , 1.9x10 ⁻⁹)
10 ¹²	1.3×10^{-8} (2.5x10 ⁻¹⁰ , 1.5x10 ⁻⁸)	1.5×10^{-8} (3.3x10 ⁻⁹ , 2.7x10 ⁻⁸)	3.9×10^{-8} (6.6x10 ⁻¹⁰ , 1.7x10 ⁻⁸)
10 ¹⁵	1.9×10^{-8} (4.9x10 ⁻⁹ , 9.2x10 ⁻⁹)	7.4×10^{-8} (7.8x10 ⁻⁹ , 2.2x10 ⁻⁷)	4.9×10^{-8} (9.8x10 ⁻⁹ , 4.8x10 ⁻⁸)

^a The 5th and 95th percentiles from the uncertainty are in parentheses.

^b An adjustment to account for total perinatal deaths (perinatal and neonatal) is in the risk characterization section.

^c The median mortality rate per serving of 1.3×10^{-8} for the intermediate-age subpopulation at the 10^{15} cfu/serving dose level, corresponds to 1 death in approximately 769,231 servings (1/1.3x10⁻⁸).

For Intermediate-Age group;

If dose = 1000 CFU, then 95% CI spans 81 orders of magnitude

If dose = 1000,000 CFU, then 95% CI spans 42 orders of magnitude

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Conversion Factor (Illness : Mortality Ratio)

Table IV-11. Reported and National Annual Projections for Severe Listeriosis, Based of FoodNet Reports

Sub-Population	National Projected Annual ^a		FoodNet Reported 4-Year Total ^b		Illness: Mortality Ratio ^c
	Cases of Listeriosis ^d	Deaths	Cases of Listeriosis ^d	Deaths	
Neonatal	216	16 ^e	38	3	12.7
Intermediate	702	67	113	10	11.3
Elderly	1159	307	194	52	3.7
TOTAL	2078	390	345	65	

^a Adjusted cases and deaths for the total population (average of 4 years FoodNet data).

^b Reported total cases and deaths for the FoodNet catchment areas (4 year total)

^c The mortality: illness ratio is calculated using the reported cases and deaths in the FoodNet catchment area, i.e., deaths divided by cases.

^d Serious cases of listeriosis requiring hospitalization.

^e Perinatal deaths = 40. Deaths for the perinatal group are calculated by multiplying the death for neonatal by 2.5 to account for abortions and stillbirths not reported in FoodNet surveillance reports. See description of the neonatal dose-response curve below.

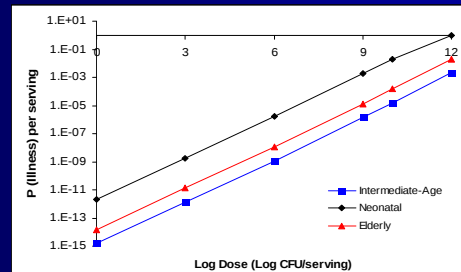
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Estimated P(ill) in Human

Mortality Ratio (Median)		11.3	12.7	3.7
Dose (CFU)	Log dose (log CFU)	Median P (Illness) per serving		
		Intermediate Age	Neonatal	Elderly
1	0	1.70×10^{-15}	2.03×10^{-12}	1.48×10^{-14}
1×10^3	3	1.36×10^{-12}	1.65×10^{-9}	1.33×10^{-11}
1×10^6	6	1.13×10^{-9}	1.65×10^{-6}	1.15×10^{-8}
1×10^9	9	1.36×10^{-6}	1.78×10^{-3}	1.26×10^{-5}
1×10^{10}	10	1.47×10^{-5}	1.91×10^{-2}	1.44×10^{-4}
1×10^{12}	12	2.15×10^{-3}	9.40×10^{-1}	1.81×10^{-2}

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Estimated P(ill) in Human



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FAO/WHO D-R for Lm

- Epidemiology based
- # of servings at 5 dose levels
From FDA Exposure Assessment
- Assumption of maximum dose level
7.5, 8.5, 9.5, and 10.5 log₁₀
- Model: Exponential
 $P = 1 - \exp^{-r \cdot N}$ (Estimation of r-values)

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FAO/WHO D-R for Lm

Data Inputs	Mean	Range
Susceptible Population (%)	17.5 %	15 – 20%
Listeriosis in susceptible population (%)	83 %	80 – 98 %
Total # of listeriosis in the US	2518	1888 - 3148

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Exposure Data used for D-R

Food Category	Total Consumption (Servings)	<1g	1-1E3g	1E3-1E6g	1E6-1E9g	>E9g	Total
Smoked Seafood	2.05E+08	70.64%	14.29%	11.06%	3.42%	0.20%	0.996
Raw Seafood	1.02E+08	92.07%	6.66%	1.21%	0.07%	0.00%	1.000
Preserved Fish	1.05E+08	84.77%	10.42%	3.89%	0.49%	0.04%	0.996
Cooked RTE Shellfish	5.52E+08	94.50%	4.01%	1.28%	0.20%	0.05%	1.000
Vegetables	1.17E+11	91.11%	7.23%	1.54%	0.07%	0.00%	1.000
Fruits	5.03E+10	81.37%	18.49%	0.13%	0.00%	0.00%	1.000
Soft mold-ripened	2.44E+08	92.81%	3.21%	3.34%	0.67%	0.01%	1.000
Goat/Sheep etc cheese	2.55E+08	92.18%	6.24%	1.48%	0.07%	0.00%	1.000
Fresh soft Cheese	1.34E+08	89.72%	3.20%	4.31%	2.51%	0.19%	0.999
Heated and Processed	1.82E+10	98.20%	1.71%	0.08%	0.01%	0.00%	1.000
Aged Cheese	1.38E+10	98.07%	1.82%	0.03%	0.00%	0.00%	0.999
Pasteurized Milk	8.72E+10	99.20%	0.74%	0.05%	0.00%	0.00%	1.000
Raw Milk	4.36E+08	91.87%	7.56%	0.55%	0.01%	0.00%	1.000
Ice Cream	1.49E+10	99.08%	0.53%	0.02%	0.00%	0.00%	0.996
Miscellaneous Dairy	2.81E+10	98.26%	1.64%	0.07%	0.00%	0.00%	1.000
Frankfurters	6.52E+09	92.40%	6.08%	1.37%	0.21%	0.02%	1.001
Dry/Semi-Dry	1.79E+09	90.27%	6.83%	2.40%	0.10%	0.00%	0.996
Deli Meats	2.07E+10	90.66%	5.40%	3.29%	0.70%	0.12%	1.002
Pate	1.18E+08	91.52%	4.01%	2.87%	1.06%	0.22%	0.997
Deli Salads, Non	5.63E+09	86.30%	8.77%	3.98%	0.80%	0.03%	0.999
Total servings	3.66E+11						

Estimation of r-values (Single Maximum-dose derived)

$$P = 1 - \exp^{-r * N}$$

$$r = -\ln(1-P) / N$$

P = # of listeriosis in the US / total # of servings at given dose
N = Assumed max log dose

Example:

- N (dose) = $8 \log_{10}$
- # of listeriosis in the US (susceptible pop) = 2090 (2518×0.83)
- Total # of servings at max dose of $8 \log_{10}$ = 5.23×10^6
- P = $2090 / 5.23 \times 10^6 = 0.0004$

$$\therefore r = -\ln(1-0.0004) / 1 \times 10^8 = 4 \times 10^{-12}$$

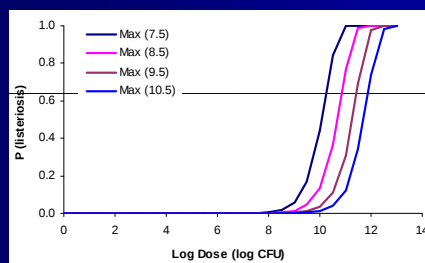
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Estimated r-values

Max. log dose	Total # of servings	r (S_Max dose-derived)
7.5	7.9×10^6	8.05×10^{-12}
8.5	3.4×10^6	1.95×10^{-12}
9.5	1.3×10^6	5.24×10^{-13}
10.5	2.5×10^5	2.61×10^{-13}

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FAO/WHO D-R for Lm



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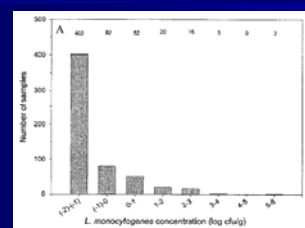
Other Lm Dose-Response

- Chen *et al.* (2003)*
 - Anchoring Approach using
 - Epidemiological data from CDC (MD & CA, 2000-2001)
 - $53 \text{ cases} \times 2 \text{ (multiplier)} = 106 \text{ cases}$
 - Food Survey data (MD&CA, 2000-2001)
 - Model: Exponential

* Journal of Food Protection, 60:918-922

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Distribution of Lm in RTE



2 year survey in MD and CA: total 577 positive samples
Beta (0.29, 2.68, -1.69, 6.1)
Gamma (0.33, 2.96, -1.7)

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Comparison of r-values

Country	r - value
US (Chen <i>et al.</i> , 2003)	1.76×10^{-10}
Germany (Buchanan <i>et al.</i> , 1997)	1.18×10^{-10}
Sweden (Lindqvist and Westoo, 2000)	5.6×10^{-10}

FAO/WHO: $r = 2.61 \times 10^{-13} \sim 8.37 \times 10^{-12}$

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Epidemiological Data for Lm

- Outbreak could occur at very low doses
 - e.g. Frankfurters: < 0.3 cfu/g
- Surveillance data: underestimated
 - Multiplier for Lm: 2 (Mead *et al.*, 1999)

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Outbreaks for Listeriosis

Location, Year (Reference)	Food Source	Serotype	Contamination Level (cfu/g)	Amount Consumed	No. Ill	Attack Rate
LA County, 1985 (Linnan <i>et al.</i> , 1988)	Mexican-style soft cheese	82% 4b	1.4×10^4 to 5×10^6	NA ^a	142	NA
Switzerland, 1983-87 (Bula <i>et al.</i> , 1995)	Soft smear-ripened cheese	75% 4b	1×10^4 to 1×10^6	NA	122	NA
IL, MO, WI, 1994 (Dallan <i>et al.</i> , 1997)	Chocolate milk	1/2b	1×10^6 (cfu/mL)	240 mL	45	45/60 (median)
Italy, 1993 (Salamina <i>et al.</i> , 1996)	Cream cheese	1/2b	460	NA	18	18/39
	Fruit tart	1/2b	0.93	NA	18	18/39
	Rice Salad ^b	NA	NA	NA	18	18/39
Finland, 1998-99 (Lyytikäinen <i>et al.</i> , 2000)	Butter	3a	< 100 ^c	NA	25	NA
Multi-state, 1998-99 (CDC, 1998b)	Frankfurters	4b	< 0.3	NA	101	NA

^a NA = Not available

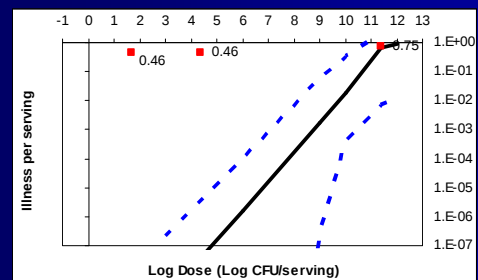
^b Rice salad implicated by epidemiology; $p < 0.001$

^c One sample contained $12,400$ cfu/g

Source: FDA/OPSS and USDA/FSIS (2003) Quantitative Assessment of Relative Risk to Public Health from Foodborne *Listeria monocytogenes* Among Selected Categories of Ready-to-Eat Foods (http://www.foodsafety.gov/~dms/lmr2-a9.html)

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FDA/FSIS DR model vs. Outbreaks



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Summary

- Both FDA/FSIS and FAO/WHO RA used an anchoring approach to predict dose-response for Lm.
- FDA/FSIS RA was used for risk ranking of RTE foods — no end-point effect
- FAO/WHO dose-response estimates: not consistent with other estimates

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Points for discussion

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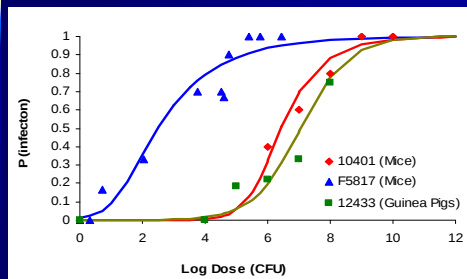
Validation of the US D-R

- If the results are similar
 - Increase the credibility of the D-Rs
- If the results are different
 - Different host-susceptibility?
 - Difference in Lm strain?
 - Flawed anchoring approach?

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Other Lm D-R approaches

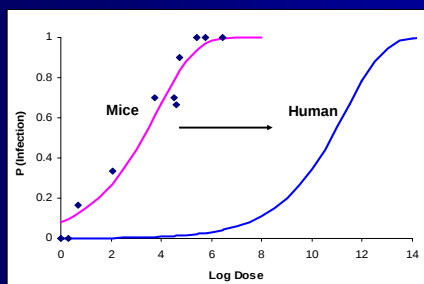
(Infection in Mice and Guinea Pigs)



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Adjustment for Humans

(Infection)



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Conversion Factor

- Infection $\Rightarrow$ Illness $\Rightarrow$ Death
- $P(\text{death} | \text{infection})$: dose-dependent

TABLE 2. Comparison of LD_{50} and ID_{50} values obtained through oral administration of *L. monocytogenes* F5817 for C57Bl/6J mice.

Dose (Log ₁₀ CFU)	#Dead/ #Inoculated	LD_{50} (95% CI) ^a	#Infected/ #Inoculated	ID_{50} (95% CI) ^b
Control	0/5		0/5	
3.74	1/10		7/10	
4.51	2/10		7/10	
4.74	4/10		9/10	
5.40	10/10		10/10	
5.74	10/10		10/10	
6.45	10/10	4.77 ^c (4.61-4.94)	10/10	3.23 ^d (1.96-4.51)

^cControl doses consisted of 0.5 ml sterile 11% NFMS (0.0 Listeria ml).

^dValues are not significantly different ($p < 0.05$).

^a95% Confidence Interval.

Golnazarian *et al.* (1989) *JFP* 52:696-701

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Conclusion

- Large uncertainty associated with Lm D-R
- No human D-R data available. Using animal D-R data to extrapolate to humans
- Incongruity between outbreak data and the dose-response models
- International interest in establishing acceptable Lm levels at consumption suggests the need for highly credible D-R estimates

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Acknowledgement

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Thank you !

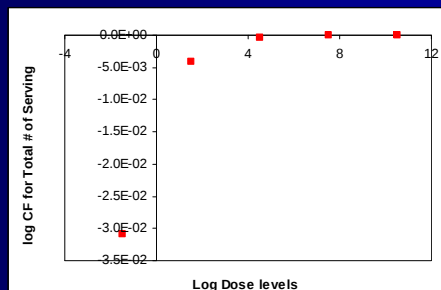
Suggestions/Comments?

or, Questions?

Better information. Better decisions. Risk assessment.

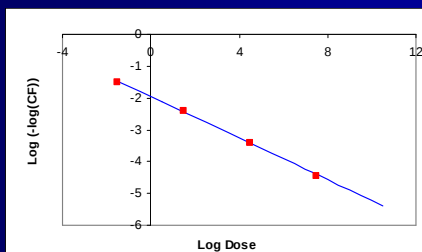
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Log Cumulative Frequency (CF) for total # of servings



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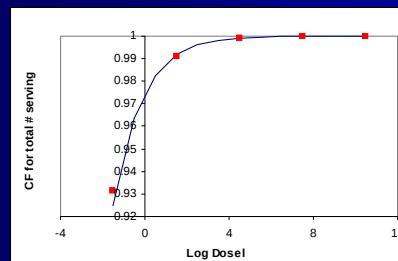
Linear Regression



$$\log \{-\log (CF)\} = K \times \log (Dose) + m; \quad K = -0.345, m = -1.869$$

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Cumulative Frequency of total # of servings



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