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Risk-Based Critical Concentrations of *Legionella pneumophila* for Indoor Residential Water Uses

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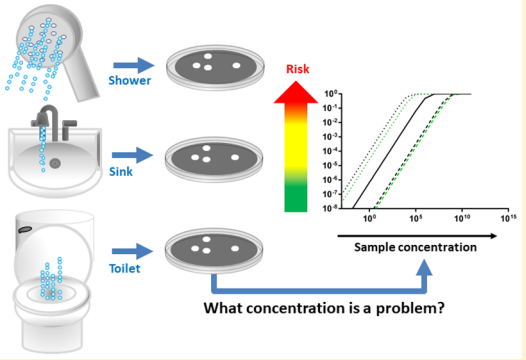
Supporting Information

ABSTRACT: *Legionella* spp. is a key contributor to the United States waterborne disease burden. Despite potentially widespread exposure, human disease is relatively uncommon, except under circumstances where pathogen concentrations are high, host immunity is low, or exposure to small-diameter aerosols occurs. Water quality guidance values for *Legionella* are available for building managers but are generally not based on technical criteria. To address this gap, a quantitative microbial risk assessment (QMRA) was conducted using target risk values in order to calculate corresponding critical concentrations on a per-fixture and aggregate (multiple fixture exposure) basis. Showers were the driving indoor exposure risk compared to sinks and toilets. Critical concentrations depended on the dose response model (infection vs clinical severity infection, CSI), risk target used (infection risk vs disability adjusted life years [DALY] on a per-exposure or annual basis), and fixture type (conventional vs water efficient or "green"). Median critical concentrations based on exposure to a combination of toilet, faucet, and shower aerosols ranged from ~10^{-2} to ~10^{0} CFU per L and ~10^{1} to ~10^{3} CFU per L for infection and CSI dose response models, respectively. As infection model results for critical *L. pneumophila* concentrations were often below a feasible detection limit for culture-based assays, the use of CSI model results for nonhealthcare water systems with a 10^{-6} DALY pppy target (the more conservative target) would result in an estimate of 12.3 CFU per L (arithmetic mean of samples across multiple fixtures and/or over time). Single sample critical concentrations with a per-exposure-corrected DALY target at each conventional fixture would be 1.06×10^{3} CFU per L (faucets), 8.84×10^{3} CFU per L (toilets), and 14.4 CFU per L (showers). Using a 10^{-4} annual infection risk target would give a 1.20×10^{3} CFU per L mean for multiple fixtures and single sample critical concentrations of 1.02×10^{5}, 8.59×10^{5}, and 1.40×10^{3} CFU per L for faucets, toilets, and showers, respectively. Annual infection risk-based target estimates are in line with most current guidance documents of less than 1000 CFU per L, while DALY-based guidance suggests lower critical concentrations might be warranted in some cases. Furthermore, approximately <10 CFU per mL *L. pneumophila* may be appropriate for healthcare or susceptible population settings. This analysis underscores the importance of the choice of risk target as well as sampling program considerations when choosing the most appropriate critical concentration for use in public health guidance.



1. INTRODUCTION

The importance of opportunistic pathogens such as *Legionella* has been increasing in recent years, with *Legionella* spp. identified in recent US Centers for Disease Control and Prevention (CDC) reports as the most common cause of waterborne disease outbreaks in the US.[1,2] *Legionella* causes illness primarily in individuals with underlying health conditions, and/or the elderly. Infection occurs when aerosols containing the bacteria are inhaled or aspirated by a susceptible host. Recent reviews of environmental sources of *Legionella* infections for sporadic and outbreak-associated cases[3−5] have emphasized the importance of building water and cooling tower design and maintenance.

Monitoring routinely for *Legionella* is not typically practiced in premise plumbing systems except when legionellosis cases

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Table 1. Guidance Values for *Legionella* spp. (*L. pneumophila* Where Noted) Concentrations in Water-Associated with Health-Based Targets or Requiring Corrective Action in Piped Water Systems, Excluding Cooling Towers and Other Aerosol Generating Devices

source	potable water (CFU per L unless specified otherwise)
Pathcon/US Occupational Safety and Health Administration (OSHA)[62]	10^4 (Action 1: Cleaning and biocide- domestic water)
	10^5 (Action 2: Cleaning and biocide, immediately prevent employee exposure- domestic water)
Pathcon Technical Bulletin 1.5[63]	Detectable but $<10^3$ (Action 1 and Action 2- review routine maintenance program recommended by manufacturer's recommended program is being followed. The presence of barely detectable numbers of legionellae represent a low level of concern. Conduct follow-up legionellae analysis after a few weeks for evidence of further amplification. This level of legionellae represent little concern, but the number of organisms detected indicates that the system is a potential amplifier for legionellae)
	10^3 to 9×10^3 (Action 3: Implement Action 1 and 2. Conduct review of premises for direct and indirect bioaerosol contact with occupant sand health risk status of people that may come in contact with the bioaerosols. Depending on the results of the review of the premises, action related to cleaning and/or biocide treatment of the equipment may be indicated. This level of legionellae represents a low but increased level of concern).
	10^4 to 9.9×10^4 (Action 4: Implement Action 3. Cleaning and/or biocide treatment of the equipment is indicated. This level of legionellae represents a moderately high level of concern. The level is approaching levels that may cause outbreaks. It is uncommon for samples to contain numbers of legionellae which fall into this category).
	$\geq 10^5$ (Action 5: Immediate cleaning and/or biocide treatment of the equipment is definitely indicated. Conduct post-treatment legionellae analysis to ensure effectiveness of the corrective action. The level of legionellae represent a high level of concern. These numbers are at a level that has the potential for causing an outbreak. It is very uncommon for samples to contain numbers of legionellae which fall in this category).
Allegheny County Health Department (ACHD) 1997[20]/Best 1983[19]	30% distal sites (Healthcare- "disinfect distribution system")[a]
French Ministry of Health[50]	Nondetectable (high-risk patients)
	250 (Alert level for high-risk patients)
	<50 (Target where at-risk patients are hospitalized)
	$<10^2$ (Target for prevention of nosocomial infections)
	$<10^3$ (General target for public facilities)
	10^3 (Alert level- patients with individual risk factors)
	10^4 (Maximum level- patients with individual risk factors)
Germany Technical and Scientific Association for Gas and Water (DVGW) 2004[50]	10^3 (Health-based target)
Netherlands Ministry of Housing, Spatial Planning and the Environment (VROM) 2002[50]	10^2 (Guideline target)
	$>10^3$ (Immediate action needed to prevent closure of (part of) system involved
UK Health and Safety Executive (HSE) 2004[50]	$<10^2$ (Guideline target)
	10^2–10^3 (Action depends on whether just one or two or the majority of samples are positive; review of control measures and risk assessment required; possible disinfection
	$>10^3$ (Immediate review of control measures and risk assessment required; possible disinfection
Lee et al.[61]/Joseph et al.[64]	Cooling towers/water in nonhealthcare premises: $< 10^3$ (Satisfactory)
	$>10^3$ (Alert)
	$>10^4$ (Action)
	5×10^3 genome units (GU) (Investigate, review control measures, culture)[b]
	5×10^4 GU (Disinfect and take other actions as recommended)
	Healthcare settings and outbreak investigation: 4×10^3 GU *L. pneumophila* (Alert) or 10^4 GU *Legionella* spp. (Alert)

[a]The 30% estimate was derived from data for a single hospital. [b]Quantitative conversion rate for genomic units to CFU not provided; target gene of qPCR assay not specified.

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are associated with a facility. While *Legionella* occurrence in premise plumbing systems is not uncommon,[6−13] monitoring for *Legionella* spp. on a routine basis may not be a cost-effective measure.[14] However, in order to validate aspects of a water safety plan or management strategy, knowledge regarding interpretation of *Legionella* spp. sampling results can provide information regarding potential risks. Concentrations of *L. pneumophila* in cold tap water have been reported up to $\sim 10^5$ gene copies per L[12,15,16] and $\sim 10^4$ colony forming units (CFU) per L,[8,10,11,17] and up to $\sim 10^7$ CFU per L in hot water.[8,18]

Existing water quality guidance values for *Legionella* spp. are available for building water quality managers to inform the interpretation of measurements made in their water systems, with potable water values ranging from 10^2 to 10^5 colony forming units (CFU) per L associated with various desired water management actions (Table 1). In one case, a French guideline specifies <50 *L. pneumophila* per L for hospitalized at-risk patients. However, these criteria generally do not have a clear technical basis and are based on judgment. In particular, the approach for using 30% positivity as a metric was based on a study of a single hospital.[19] This metric was caveated in the Allegheny County guidance document, citing it as an "arbitrary" value for a decision point.[20] Approaching the setting of concentration criteria using a risk-based approach would be beneficial for comparison with established concentration limit recommendations. This study uses a quantitative microbial risk assessment (QMRA) approach in which target risk values for infection (10^{-4} annual probability of infection[21] and 10^{-6} disability adjusted life years per person per year, i.e., DALY pppy[22]) are used to calculate corresponding environmental exposures for indoor fixture use scenarios. Exposures to aerosols from water fixtures in the indoor environment are considered for multiple scenarios and human susceptibilities to identify the most important factors driving the risk estimate. These results can help to provide context for *Legionella* spp. concentration measurements and identify potential data gaps for larger-scale risk prioritization and modeling efforts.

The QMRA framework can be used to evaluate the human health risks associated with exposure to a particular pathogen given a pathogen occurrence, exposure scenario, health endpoint, and population at risk.[23] The QMRA makes use of dose−response functions linking the degree of exposure with a probability of an adverse effect; dose−response functions are useful for quantifying risks at low doses (due to low concentrations present in the environment, low potential for exposure, or a combination of these factors), especially as interpreting low-dose exposures can be challenging using epidemiological information due to the need for large studies to detect a small effect size. Multiple dose−response functions are available for *Legionella* spp., where the two most commonly used are for "clinical severity infection (CSI)" and "sub-clinical infection (infection)" endpoints for *L. pneumophila*.[24,25] The "sub-clinical infection" dose response model could also potentially be used to represent a Pontiac fever infection endpoint.[30,31] Additionally, a time-dependent model for *L. longbeachae* has also been utilized to model *L. pneumophila* risks, demonstrating plausible concordance with observed outbreak information from well-documented Legionnaires' disease outbreaks in Melbourne and Japan.[26] While there are over 50 species of *Legionella* and several are human pathogens, the most commonly identified cause of legionellosis (including Legionnaires' disease and the less severe form of illness, Pontiac fever) is *L. pneumophila*.[27,28]

Previously, a framework for *Legionella* QMRA has been developed,[29] accounting for *Legionella* generation and partitioning in aerosols, fate and transport, and infection processes. This approach was applied to a variety of water uses.[30,31] The indoor uses of water previously assessed included showers[32] and toilets,[30,31] but a critical concentration has not yet been calculated for exposure to multiple fixtures in an indoor environment. Faucet exposure was not previously considered. The only available model for a critical concentration of *Legionella* was for a single showering event, with critical concentrations ranging from 3.5×10^6 to 3.5×10^8 CFU per L.[32] The single-shower estimates were calculated using a target deposited dose of 1−100 CFU, rather than relying upon a dose response model function or explicit target risk for *L. pneumophila*. The concentration of *Legionella* in bulk water is the focus of the current analysis as biofilms are less likely to be sampled in routine practice compared to bulk water in plumbing systems. The concentration in bulk water simulated in this analysis includes the contribution of sloughed-off biofilm-associated *Legionella*.

Previously, low-flow and water saving fixtures have been shown to produce varying aerosol size profiles;[33−35] the impact of such distinctions are evaluated here to assess the extent to which building type (for example, "green" or Leadership in Energy and Environmental Design [LEED] buildings) can influence critical concentrations. This is of great importance as motivations for increasing sustainability of the built environment may create opportunities for pathogen growth or management difficulties in premise plumbing systems.[36,37]

Given the need to suggest defensible water quality criteria values for *Legionella* spp., especially for *L. pneumophila*, the goals of the current study are to (1) develop risk-based *L. pneumophila* concentration values in water associated with established target risk values using QMRA for a set of exemplary exposure scenarios; (2) compare modeled values to existing guidance information; and (3) suggest research gaps for applying these approaches to various building water scenarios, given known heterogeneity in systems, human activity patterns, susceptible populations, and intended water uses. It is acknowledged that most outbreaks of legionellosis occur in healthcare settings,[5] however, the primary intent of this analysis is to evaluate the plausibility of setting limits on *L. pneumophila* concentrations under a variety of circumstances.

2. MATERIALS AND METHODS

2.1. Exposure Models. A *Legionella* spp. infection can result from exposure to aerosols or aspiration. Due to a lack of quantitative information regarding aspiration rates in the literature, the focus of this analysis was on inhalation of aqueous aerosols produced by common water fixtures. While exposure to aerosols can occur in various building water environments such as residential, commercial, and healthcare buildings, models were developed for a residential environment as a starting point as summary information was not readily available regarding activity and exposure patterns in healthcare facilities. In residential buildings, rates of usage for water fixtures have been documented.[38,39] Of the fixtures for which usage information is available (toilets, showers, faucets,

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Table 2. Monte Carlo Exposure Parameters Common to All Models

parameter	symbol	unit	value	distribution	source
Breathing rate, light activity, breathing cycle period 8 s and 1 L tidal volume	B	m^3 per min	0.013−0.017	Uniform	65
Deposition efficiency for aerosols of MMAD[b] i	D_i	Fraction			
1			Min = 0.23, Max = 0.25	Uniform (Nasal, Oral)	66
2			Min = 0.40, Max = 0.53		
3			Min = 0.36, Max = 0.62		
4			Min = 0.29, Max = 0.61		
5			Min = 0.19, Max = 0.52		
6			Min = 0.10, Max = 0.4		
7			Min = 0.06, Max = 0.29		
8			Min = 0.03, Max = 0.19		
9			Min = 0.01, Max = 0.12		
10			Min = 0.01, Max = 0.06		
Percentage of total aerosolized Legionella in aerosols of MMAD[b] i	F_i	%		Point	40
1			17.50		
2			16.39		
3			15.56		
4			6.67		
5			3.89		
6			2.50		
7			2.78		
8			5.00		
9			5.28		
10			3.89		
Dose response parameter for *L. pneumophila*, infection endpoint	r_{inf}	Unitless	$\mu = -2.93$, $\sigma = 0.49$	Lognormal[a]	24,67
Dose response parameter for *L. pneumophila*, clinical severity infection endpoint	r_{csi}	Unitless	$\mu = -9.69$, $\sigma = 0.30$	Lognormal	24,68
DALYs per *Legionella* infection	DALY/infection	DALYs/legionellosis case	0.97	Point	47

[a]Lognormal parameters mean, standard deviation (μ, σ) calculated from population (normal) parameters ($\bar{x}$, s) using standard formulas as follows: $\mu = \ln(\bar{x}^2/(s^2 + \bar{x}^2)^{1/2})$, $\sigma = [\ln(1 + (s^2/\bar{x}^2))]^{1/2}$, where $\bar{x}$ is the sample mean and s is the sample standard deviation. [b]MMAD = mass median aerodynamic diameter in μm.

clothes washers, bathing, and dishwashers), the three uses likely to constitute the majority of aerosol exposures were chosen for this analysis: faucet, toilet, and shower aerosols, each of which is described below. Exposure was considered on the basis of exposures to each individual fixture, as well as an aggregated scenario where exposure to a combination of fixtures is considered in a typical indoor household environment. The usage data available[38,39] do not distinguish between kitchen-, bathroom-, or other associated-water fixture exposures and the analysis therefore did not distinguish between specific locations of the water fixtures within the models.

2.2. Indoor Water Fixture Exposure Scenarios. The inhalation of water sprays was considered using two types of exposures, one via a partitioning coefficient (eq 1), and one method considering the aerosol size profile of each water fixture where such information was available (eq 2).[29−31] In the former approach, a ratio of *L. pneumophila* observed in water and air (reported in CFU m^{-3}/CFU L^{-1}) was computed. In the latter approach, the volume of aerosols of various size diameters that are large enough to hold *L. pneumophila* bacteria but small enough to deposit at the alveoli (1 μm < diameter <10 μm) were considered.

$$\text{dose}_{\text{fixture}} = C_{\text{Leg}} PBtF_iD_i \quad (1)$$

$$\text{dose}_{\text{fixture}} = C_{\text{Leg}} Bt \sum_{i=1}^{10} C_{aer,i} V_{aer,i} \sum_{i=1}^{10} F_iD_i \quad (2)$$

where C_{Leg} = the concentration of *L. pneumophila* bacteria in water at the fixture; $C_{aer,i}$ = the concentration of aerosols [#/m^3] of diameter i where i = 1:10 μm, $V_{aer,i}$ = the volume of aerosol for size bin i calculated as $V = (4/3)\pi\,(i/2 \times 10^{-6})^3$, P = the partitioning coefficient (CFU/L^{-1}/CFU m^{-3}); B = breathing rate (m^3/min), t = exposure duration (min); D = alveolar deposition efficiency of size i diameter aerosols; and F_i = the fraction of *L. pneumophila* that partitions to the applicable size diameter aerosols (either that reported in the data used to calculate the partitioning coefficient for faucets over a 1−8 μm diameter bin[44] or fractions reported by Allegra, et al.[40]) (Table 2). Where data for aerosol size from a given activity spanned multiple size bins (for example, for showers, aerosols were measured over ranges 1−2 μm, 2−3 μm, 3−6 μm, and 6−10 μm), the deposition efficiency (D_i, available for each individual size aerosol 1−10 μm) was simulated using the lower and upper bound of all D_i values in the size range of interest. For example, for the [6,10) bin, a uniform distribution was developed with the lowest D_i and highest D_i observed for bins 6, 7, 8, 9, and 10 [$D_i \sim$ uniform(0.01, 0.29)] (Table 2). The aerosol diameter was simulated for each bin as a uniform distribution ranging over the bin diameters, i.e., for [6,10) diameter $i \sim$ uniform(6,10)

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Table 3. Monte Carlo Exposure Input Parameters for Shower Exposure Scenario

parameter	symbol	unit	value	distribution	source
Shower duration	t_{sh}	min per day	μ = 7.8, σ = 0.02 (left-truncated at zero)	Normal	39
Showers per day	f_{sh}	# per day	0.69	Point	39
Exposures per year	n_{sh}	Number per year	365	Point	Assumption
Concentration of conventional fixture aerosols of diameter i:[b,c]	$C_{aer,i}$	# aerosols per m^3 of air		Lognormal[a]	33,34
[1,2)			μ = 17.5, σ = 0.30		
[2,3)			μ = 17.5, σ = 0.17		
[3,6)			μ = 19.4, σ = 0.35		
[6,10)			μ = 20.0, σ = 0.31		
Concentration of water efficient fixture aerosols of diameter i:	$C_{aer,i}$	# aerosols per m^3 of air		Lognormal	33,34
[1,2)			μ = 18.1, σ = 0.57		
[2,3)			μ = 17.9, σ = 0.64		
[3,6)			μ = 18.7, σ = 0.52		
[6,10)			μ = 18.3, σ = 0.14		

[a]Lognormal parameters mean, standard deviation (μ, σ) calculated from population (normal) parameters ($\bar{x}$, s) using standard formulas as follows: $\mu = \ln(\bar{x}^2/(s^2 + \bar{x}^2)^{1/2})$, $\sigma = [\ln(1 + (s^2/\bar{x}^2))]^{1/2}$, where $\bar{x}$ is the sample mean and s is the sample standard deviation. [b]MMAD = mass median aerodynamic diameter in μm. [c]Shower aerosol size diameters defined using uniform distributions over the stated intervals when calculating volume of water in the size bin.

Table 4. Monte Carlo Exposure Input Parameters for Toilet Flushing Scenario

parameter	symbol	unit	value	distribution	source
Toilet flushes per day	f_t	Flushes per day	5.0	Point	39
Time in bathroom after flush	t_t	Min per flush	Min = 1, Max = 5	Uniform	46
Exposures per year	n_t	Number per year	365	Point	Assumption
Concentration of aerosols for conventional toilet (pre-FEPA toilet) with MMAD[b] i:	$C_{aer,i}$	# aerosols per m^3 air		Point	31,42
1			7.43×10^4		
2			6.73×10^4		
3			6.13×10^4		
4			6.03×10^4		
5			6.12×10^4		
6			6.03×10^4		
7			5.94×10^4		
8			5.88×10^4		
9			5.80×10^4		
10			5.68×10^4		
Concentration of aerosols for water efficient toilet (averaged over 3 post-FEPA toilets) with MMAD[b] i[c]:	$C_{aer,i}$	# aerosols per m^3 air		Lognormal[a]	31,42
1			μ = 10.4, σ = 0.98		
2			μ = 10.3, σ = 0.97		
3			μ = 10.2, σ = 1.00		
4			μ = 10.1, σ = 1.01		
5			μ = 10.1, σ = 1.01		
6			μ = 10.1, σ = 1.00		
7			μ = 10.1, σ = 1.00		
8			μ = 10.1, σ = 1.01		
9			μ = 10.1, σ = 1.01		
10			μ = 10.1, σ = 1.01		

[a]Lognormal parameters mean, standard deviation (μ, σ) calculated from population (normal) parameters ($\bar{x}$, s) using standard formulas as follows: $\mu = \ln(\bar{x}^2/(s^2 + \bar{x}^2)^{1/2})$, $\sigma = [\ln(1 + (s^2/\bar{x}^2))]^{1/2}$, where $\bar{x}$ is the sample mean and s is the sample standard deviation. [b]MMAD = mass median aerodynamic diameter. [c]Concentrations of aerosol computed using average and standard deviation parameters across toilet types of Table 1 # Aerosols/m^3 * Fraction of aerosols of MMAD i; All concentrations and efficiencies listed by integer MMAD; bins considered for MMAD 1 through 10 were [0.5,1.5), [1.5,2.5), [2.5, 3.5), [3.5,4.5), [4.5, 5.5), [5.5, 6.5), [6.5, 7.5), [7.5, 8.5), [8.5, 9.5), [9.5, 10.5).

for the purposes of calculating V_{aer} in eq 2. For each parameter used in Tables 2, 3, 4, and 5, the difference in parameter transformations is indicated in the table footnote; for example, a lognormal mean and standard deviation of LN(17.5, 0.30) corresponds to an arithmetic mean of ~4 × 10^7 aerosols per m^3 air and not a mean of 17.5 aerosols per m^3 air.

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Table 5. Monte Carlo Exposure Input Parameters for Faucet Exposure Scenario

parameter	symbol	unit	value	distribution	source
Sink uses per day	f_{sink}	Number per day	20	Point	39
Sink use duration	t_{sink}	min per use	0.5	Point	39
Exposures per year	n_{sink}	Number per year	365	Point	Assumption
Sink partitioning coefficient	P_{sink}	CFU m^{-3}/ CFU L^{-1}	$\mu = -13.3$, $\sigma = 3.49$ truncated on interval $[0, 2.35 \times 10^{-3}]$	Lognormal[a]	44
Percentage of aerosols in respirable range (between 1 and 8 μm reported) for partitioning coefficient	F_{1-8}	%	50	Point	44

[a]Lognormal parameters mean, standard deviation (μ, σ) calculated from population (normal) parameters ($\bar{x}$, s) using standard formulas as follows: $\mu = \ln(\bar{x}^2/(s^2 + \bar{x}^2)^{1/2})$, $\sigma = [\ln(1 + (s^2/\bar{x}^2))]^{1/2}$, where $\bar{x}$ is the sample mean and s is the sample standard deviation.

2.3. Literature Review and Data Analysis for Exposure Parameters. The aerosol size distributions for aerosols of diameters 1−10 μm from toilet flushing and showering were available for both conventional and water saving ("efficient") water fixtures. Two types of showerheads were analyzed by O'Toole et al.,[33,34] including an Interbath Watersaver series showerhead operated at 7 L per min ("low flow", "green", or "efficient" fixture) and a Bastow Fjord conventional showerhead operated at 13 L/min ("conventional"). The Interbath fixture met water-efficient device criteria for Australian Water Efficiency Labeling and Standards (WELS) scheme of "3 stars"; above this rating requires a performance test. The conventional showerhead was operated at conditions with a WELS "1 star" rating.[34] An experimental bathroom setup with a mannequin to simulate the presence of a human was used with an aerodynamic particle sizer (APS) to quantify the number of aerosols in diameter size bin 0.2−1 μm, 1−2 μm, 2−3 μm, 3−6 μm, 6−10 μm, and 10−20 μm during a shower event at water temperatures of 38 and 42 °C. Data for the higher-aerosol producing experiments were chosen (42 °C) (Table 3). Shower temperatures in the United States have reported to range from 38 °C (101 °F) to 41 °C (106 °F),[41] and we have therefore chosen data obtained under plausible conditions on the higher end of this range.

For toilet flushing, point estimates for aerosol size distribution from a conventional pre-1992 Federal Energy Policy Act (FEPA) toilet was used with 13.3 L per flush[42] and compared to aerosol size data from three types of water efficient toilets (dual flush HET, dual-flush pressure-assisted gravity flow, and a flushometer toilet) ranging from 3.8 to 5.3 L per flush. Prior to the FEPA, US toilets typically had flush volumes of 11 to 13 L per flush but have since been decreased to 6 L per flush.[42] The fraction of aerosols in each mass median aerodynamic diameter size bin i (diameter 1 to 10 μm) produced during a toilet flush was determined from Johnson et al.[42] This fraction was multiplied by (total number of particles generated per flush [#])/(total air sampling volume [m^3]) to obtain the concentration of aerosols in each size bin (C_{aer}). These data are summarized in Table 4 and raw data used to make these calculations in the current study was previously tabulated by Hamilton et al.[31]

For faucets, an aerosol size distribution was not available and as a result, a partitioning coefficient (P) approach was used. Only one study provided this information. Previously, a partitioning coefficient for faucets of 5.6×10^{-4} was calculated by Hines et al.[43] from a data set of 19 paired water and air samples from 14 hot-water faucets with an Anderson 1 AFCM viable particle sizing sampler and BCYE agar. No information was provided regarding the specific faucet fixture in the original reference and bacteria concentrations in water were obtained by culturing 1 week prior to air sampling, not on the day of air sampling. Of the 19 water samples, 17 grew *L. pneumophila*. The authors computed an average coefficient using only the observations from which air samples had a positive concentration of *L. pneumophila* (Hines et al.[43] Table 1). However, this approach did not account for samples where *L. pneumophila* was detected in water but not in air (below the detection limit of the air sampling method). To address this issue, an interval- censored distribution was fit to the partitioning coefficient data, censoring between zero and the lowest observed coefficient in samples for which *L. pneumophila* could be measured (cultured) in air (1.32×10^{-5} L/m^3). This resulted in a computed partitioning coefficient with lognormal parameters $\mu = -13.33$, $\sigma = 3.49$, corresponding to a mean and standard deviation of 5.73×10^{-4} and 0.022, respectively. According to Bollin et al.,[44] 50% of recovered aerosols were between 1 and 8 μm in diameter; therefore, a partitioning factor of $F_i = 0.5$ was applied in eq 1 (Table 5).

2.4. Dose Response. The exponential dose−response model was used (eq 3).[23,45] Exponential dose response model parameters for *L. pneumophila* infection are provided in Table 2.[24,25]

$$P_{inf,daily} = 1 - e^{-rd} \tag{3}$$

where $P_{inf,daily}$ = daily probability of infection, d = daily dose, and r is a parameter of the exponential dose−response model. Additionally, the probability of infection was converted to a disability adjusted life year (DALY) metric using eq 4.[46] van Lier et al.[47] derived a value of 0.97 DALYs per case of legionellosis from disease surveillance statistics available from The Netherlands through the Burden of Communicable Diseases in Europe (BCoDE) project.[48] As a legionellosis case can include both Legionnaires' disease and Pontiac fever[49] and a distinction was not stated in the study, the DALY metric was simulated for both the *L. pneumophila* infection and CSI dose response endpoints to provide a DALY estimate. These two common dose response models have previously been used within a QMRA analysis to represent a subclinical infection (or potentially Pontiac Fever) and clinical-severity infection (requiring an individual to seek health care resources or medical attention).[24,25]

$$DALY_j = \frac{DALY}{infection} P_{inf,ann} \tag{4}$$

2.5. Risk Characterization. Annual infection and CSI risks were calculated as per eq 5.

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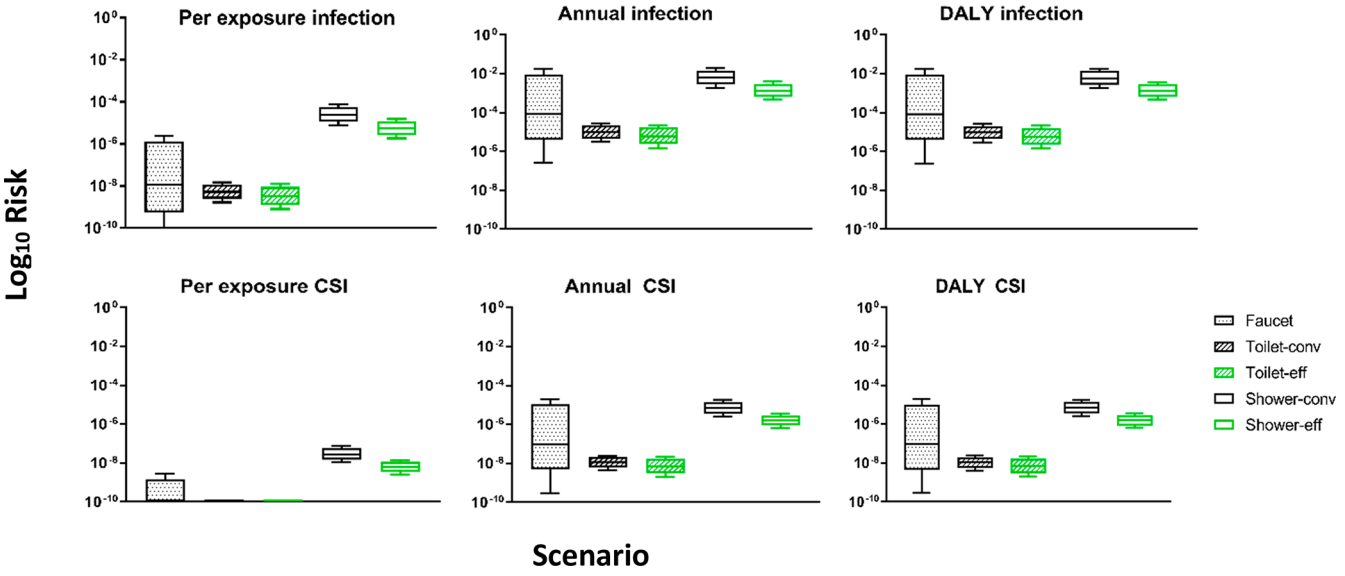

Figure 1. Annual risks by fixture with *L. pneumophila* concentration 100 CFU per L. DALY risks are on an annual basis.

$$P_{\text{inf,ann}} = 1 - \prod_{1}^{nf_j} (1 - P_{\text{inf,daily}}) \quad (5)$$

where n is the yearly frequency and f is the daily frequency of the activity j. Risks were simulated: (1) comparing annual risks for each fixture for a hypothetical concentration of 100 CFU/L that aligns with the lower end of the range of target concentration[50] guidance values for *Legionella* spp.; and 2) over a range of point estimates for *L. pneumophila* concentration. The concentration associated with a target risk of 10^{-4} annual probability of infection[21] or DALY metric of 10^{-6} infections pppy[22] was calculated based on the latter simulation of risks over a range of point estimates for *L. pneumophila* concentration. Additionally, as the fraction of exposure events (or days) at which *L. pneumophila* would be present is unknown, theoretical lower and upper bound concentrations were considered using an approach of identifying critical concentrations associated with multiple risk target values. For annual comparisons, it was assumed that *L. pneumophila* would be present over all exposure events. Additionally, in the absence of information regarding the relationship between *L. pneumophila* concentrations at the various fixtures (contamination could be entirely localized to one fixture or alternatively could be indicative of a more systemic premise plumbing issue), per-fixture simulations were also compared to an exposure-corrected target annual risk value [Annual risk target/(365 × daily fixture use frequency]. This approach has not been previously used for QMRA but is suggested here as a potential method for consideration given the complexities associated with evaluating premise plumbing microbiological risks. If *L. pneumophila* is only present during a single exposure event over the course of a year, then annual risk targets could be compared to a per-exposure risk, providing a "lower bound". Risks were also computed on a per-exposure basis to provide some basis of comparison with previous estimates.

In addition to annual risks for each exposure scenario, total, fixture-aggregated annual infection risks for each population were calculated according to eq 6. A similar approach has been used to pool risks from multiple pathogens by previous QMRA studies,[51−53] including respiratory risks due to *L. pneumophila*.[30]

$$P_{\text{inf,ann,total}} = 1 - \prod_{1}^{j} (1 - P_{\text{inf,ann},a_j}) \quad (6)$$

where $P_{\text{inf,ann,total}}$ = the total annual risk incurred from exposure to a combination of j scenarios where j = faucet, toilet, or shower exposure.

A sensitivity analysis was conducted to identify variables contributing to variability and uncertainty in annual infection and CSI risk per fixture using 10^5 Monte Carlo iterations and with the seed value set at 10^5. All computations were performed in R v.3.5.2. (www.rproject.org) and using the mc2d package.[54] The Spearman rank correlation coefficient was used to identify the most important predictive factors of annual infection or clinical severity infection risk, where 0 indicates no influence and −1 or +1 indicates that the output is wholly dependent on the given input. The model inputs were ranked based on the absolute value of their correlation coefficient with the output variable, annual risk. Interval-censored distributions for partitioning coefficient data analysis were fit using the fitdistrplus package in R (see section 2.3).[55]

3. RESULTS

Annual risks for a hypothetical concentration of 100 CFU per L *L. pneumophila*, the lowest concentration benchmark for a general population, are shown in Figure 1. While shower risks were highest, faucet risks demonstrated the highest degree of variability and/or uncertainty for annual infection risk, annual CSI risk, and the DALY metrics for infection and CSI. Risks were slightly less for low flow water efficient fixtures as these produced fewer aerosols in the respirable range. At a 100 CFU per L concentration level, median annual infection risks ranged from 5.98×10^{-6} for efficient toilets to 6.09×10^{-3} for conventional showers. When considering an aggregated exposure scenario for all three fixtures, the median annual infection risk was 1.88×10^{-3} (efficient) to 7.22×10^{-3} (conventional). Median annual CSI risks ranged from 6.98×10^{-9} for water efficient toilets to 7.14×10^{-6} for conventional showers. Median DALY risks using an infection dose response

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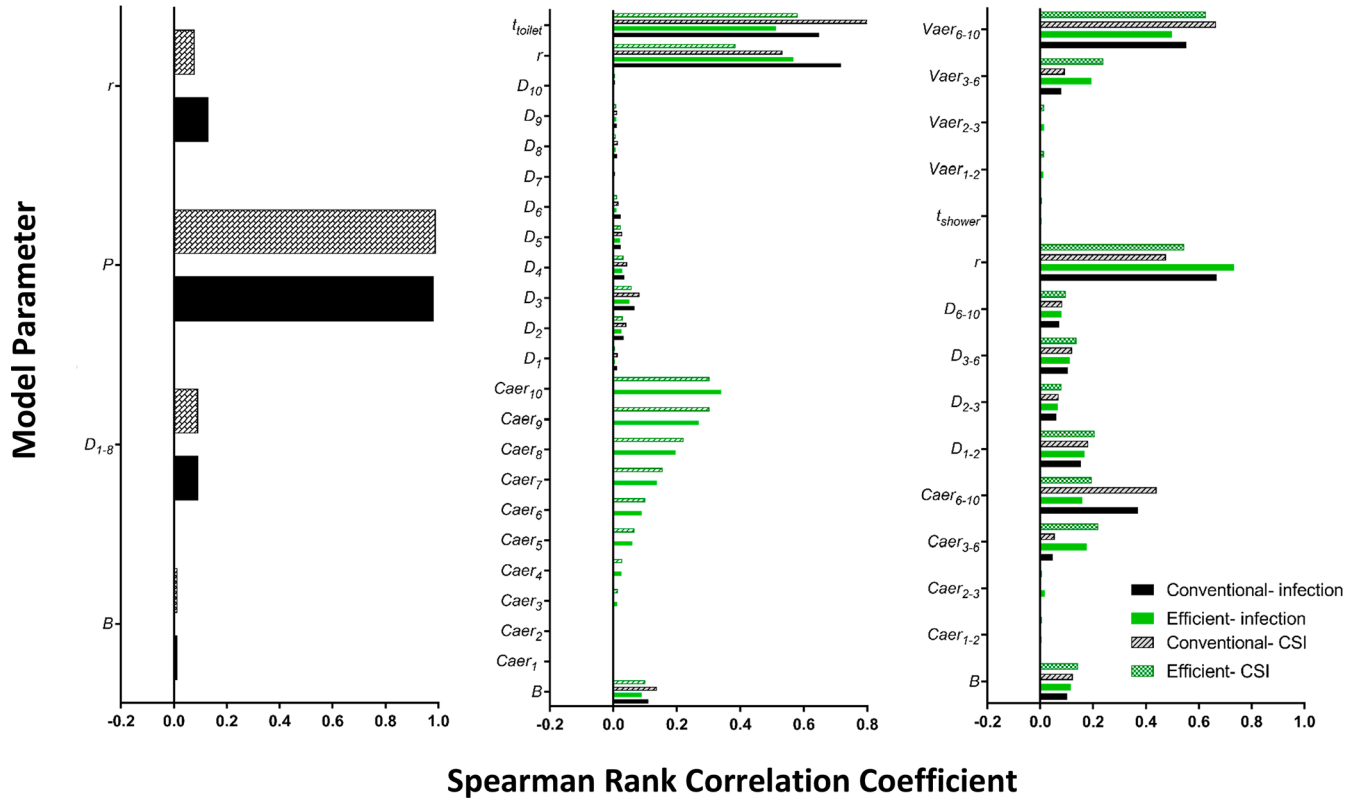

Figure 2. Sensitivity analysis for annual infection and CSI risks by fixture with *L. pneumophila* concentration 100 CFU per L. Variables are defined in Tables 2 through 5.

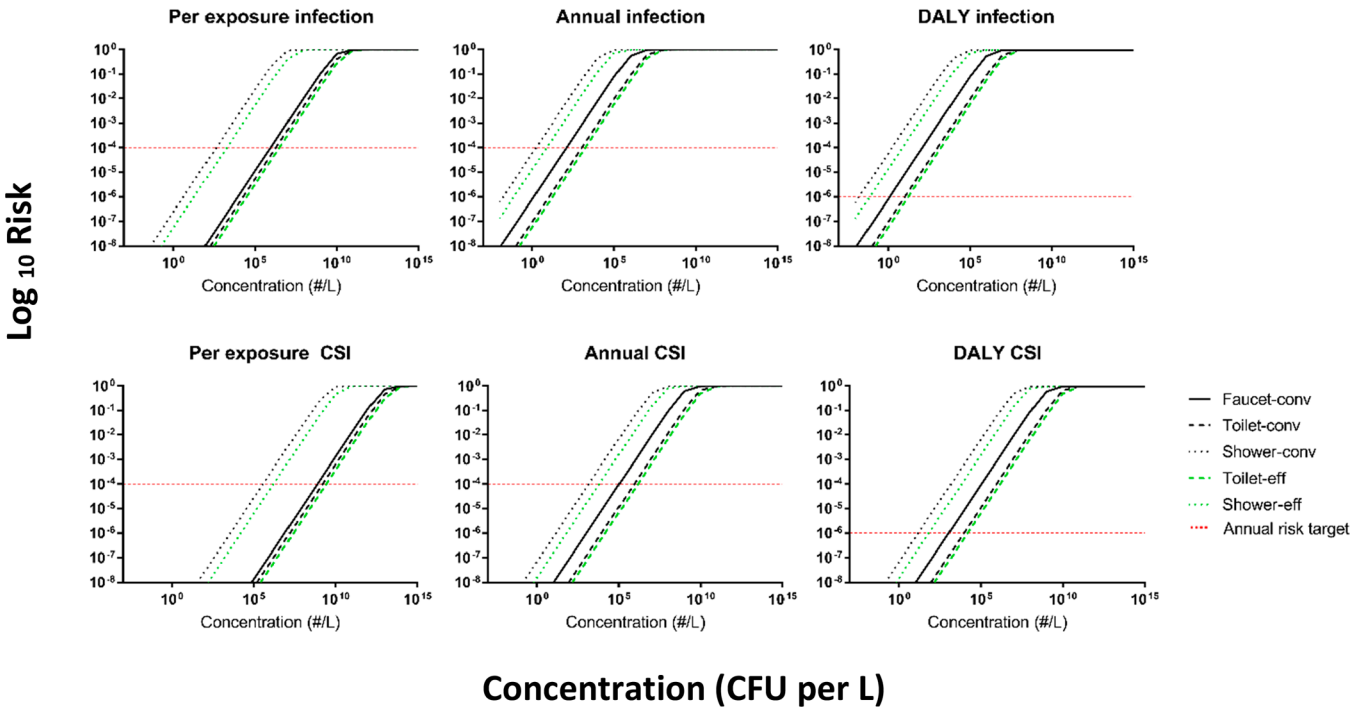

Figure 3. Median risks as a function of *L. pneumophila* concentration for various risk benchmarks

and CSI dose response model ranged from 5.80×10^{-6} (toilet, efficient) to 5.90×10^{-3} (shower, conventional) and 6.77×10^{-9} (toilet, efficient) to 6.92×10^{-6} (shower, conventional), respectively. Median DALY annual aggregated risks ranged from 2.09×10^{-6} (CSI, efficient) to 7.00×10^{-3} (infection, conventional).

For the faucet risk scenario, the most influential model parameter, as indicated by the Spearman correlation with risk, was the partitioning coefficient (P) (Figure 2) (ρ = 0.98 to

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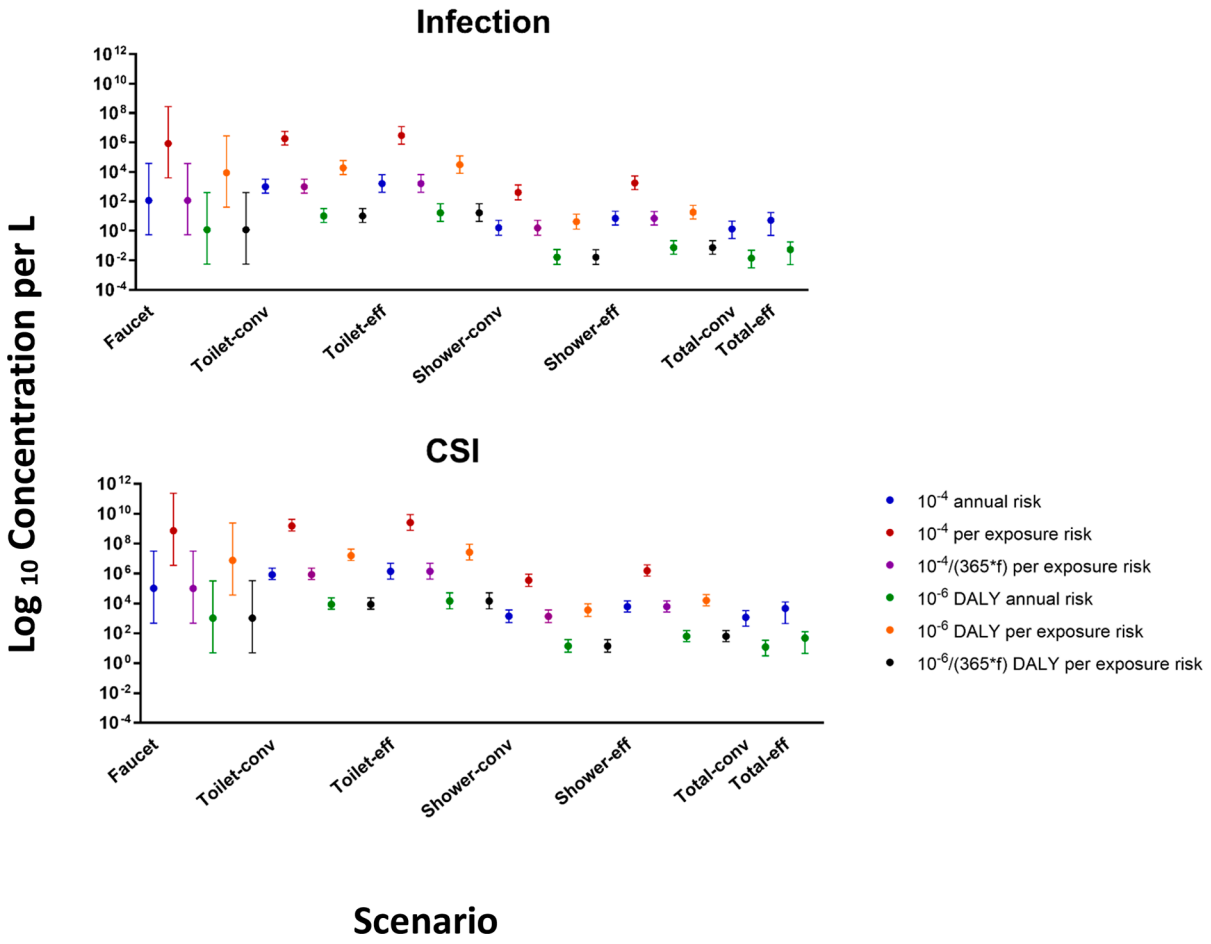

Figure 4. Critical concentrations of culturable *L. pneumophila* associated with various risk benchmarks.

0.99). For toilets and showers, the dose response parameter (r) was one of the most influential predictors with Spearman rank correlation coefficients ranging from 0.39 to 0.73 for conventional and efficient fixture scenarios. The concentration ($C_{aer,i}$) (ρ of up to 0.44 for showers, up to 0.34 for toilet flushing) and volume ($V_{aer,i}$) (ρ up to 0.67 for showers) of aerosols in various size bins were also important predictor variables. For toilet flushing, the exposure time (ρ = 0.51 to 0.80) ranked highly.

A risk profile simulated over different point estimate concentration values for *L. pneumophila* is shown in Figure 3. A comparison of per exposure (single exposure event) infection and annual infection risk (assuming *L. pneumophila* is present at an average dose over all exposures) in Figure 3 demonstrates the large impact of varying the number of exposures for determining *L. pneumophila* risks, shifting the curve to the left (decreasing the critical concentration) for annual risk roughly ~3 orders of magnitude.

Critical concentrations on a per-exposure or average annual basis to meet various risk metrics are summarized in Figure 4 and tabulated in Supplemental Table S1. Median target concentrations varied by several orders of magnitude depending on the dose response parameter, risk target, and fixture type (conventional or efficient) used. For combined exposure to multiple conventional household fixtures ("Total-conv"), median critical concentrations based on an infection dose response model would range from 1.42×10^{-2} *L. pneumophila* CFU per L (10^{-6} DALY annual target metric) to 1.38 CFU per L (annual infection of 10^{-4} target metric). For water efficient fixtures ("Total-eff"), median critical concentrations based on an infection dose response model would range from 5.46×10^{-2} CFU per L (10^{-6} DALY annual target metric) to 5.32 CFU per L (annual infection of 10^{-4} target metric). Using a CSI dose response model, median critical concentrations would range from 1.23×10^{1} CFU per L (annual DALY target) to 1.20×10^{3} CFU per L (annual infection target) for conventional fixtures ("Total-conv") and 4.81×10^{1} CFU per L (annual DALY target) to 4.67×10^{3} CFU per L (annual infection target) for water efficient fixtures ("Total-eff").

Although QMRA annual risk targets are sometimes compared to per-exposure risks in practice and such a comparison can provide useful information, it would perhaps be preferable to compare per-exposure risks to a per-exposure (scaled) risk target. To address this gap, exposure-corrected risk targets were also used ("Annual risk target/($365 \times f$)") to obtain potential fixture-specific single sample critical concentrations in Figure 4 and Supplemental Table S1. The difference in critical concentration for a given fixture decreased up to 4 orders of magnitude when making this correction, depending on the frequency of a given behavior. For example, for faucet use, the median critical concentration with a 10^{-4} per-exposure infection risk target was 8.76×10^{5} CFU/L compared to a median of 119 CFU/L with a $10^{-4}/(365 \times f_{faucet})$ risk target level as there were 20 faucet uses estimated per day (f_{faucet} = 20). For showers, this difference

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was less pronounced but still ~2 orders of magnitude as there is approximately one shower taken per day in the models.

Due to an unknown degree of heterogeneity among distal areas of the premise plumbing system both spatially and temporally, the aggregate and per-fixture risk estimates, as well as the per-exposure and annual risk estimates, may serve as bounds for a critical concentration estimate to be measured (cultured) at a particular location in a building water system. In between these two scenarios, clearly many combinations of *L. pneumophila* occurrence in space and time at all three fixtures would be possible. Fixture-specific longitudinal occurrence information could be included in this model by correcting the exposure frequency parameter f according to a proportion or distribution of proportions descriptive of the potential for *L. pneumophila* to be present during a usage event.

4. DISCUSSION

Legionella spp. infection risk continues to be a driving concern for managing water quality in building or premise plumbing systems due to the abundance of outbreaks attributable to this pathogen, especially to *L. pneumophila* serogroup 1.[5] Although guidance values are available for interpreting *Legionella* spp. sampling results, these criteria are generally not developed using a defined technical basis, but rather based on professional judgment and approximate correspondence with epidemiological findings. While a percentage of positive samples or concentration level cannot be the sole factors for evaluating safety of water in a premise plumbing system, critical concentration values associated with a target risk level can be helpful for validating a water safety plan or providing context for sampling results.

The choice of a target risk value in this analysis was based on commonly accepted targets of 10^{-4} annual risk of infection or 10^{-6} DALYs pppy. However, the selection of this target is a value judgment, and would benefit from additional decision analysis. Target health risk levels are not the only consideration for water quality in premise plumbing, and water quality managers and policy makers could consider target health risk benchmarks within the context of a more comprehensive strategy to manage costs, energy, logistical concerns, and site-specific requirements. Generally, using a DALY metric as a target risk threshold will result in a lower (more stringent) critical concentration of *Legionella* in premise plumbing compared to an infection risk benchmark. Similarly, an infection dose response model calculation will result in lower target risks compared to a CSI dose response model calculation. The critical concentration values derived in the current analysis are highly dependent on a number of factors including the dose response model upon which the calculation is based, exposure parameters, and target risk benchmark. In terms of fixtures driving risks, showers > faucets > toilets.

It is noted here that previous assessments have demonstrated that the appropriate measure of risk is the average of multiple exposures.[56] Therefore, when few data are available in the literature to assess the time variability of *L. pneumophila* concentrations and doses as in the current case, the annual exposure dose in this study can be regarded as a time-averaged arithmetic dose even if time variability is significant.[23,45] Consequently, while critical concentration values calculated in association with per-exposure scenarios might be interpreted as a single sample concentration, critical concentration values associated with annual risk scenarios might be interpreted as average concentrations over multiple sampling events. A major limitation of the guidance documents summarized in Table 1 is that specific sampling locations, frequency and timing of samples taken at a given location, and statistically rigorous interpretation of sampling results is not specified. Simulating a full three-dimensional space for concentration, exposure frequency, and risk is recommended as a follow-on to this analysis and could help to customize risk findings to sampling results observed at a particular building or other setting.

As demonstrated here (Figure 4), the ultimate decision regarding concentration limit values is a function of which risk target is used (e.g., 10^{-4} annual probability of infection or 10^{-6} DALY pppy). Therefore, an analysis of how timing and extent of sampling might affect critical concentration conclusions is beyond the scope of the current set of models but is recommended for further analysis. As actions within the context of a water management plan are typically developed on a case-by-case basis, the current modeling approach can allow for lower-risk facilities to adopt different cut-offs for action.

For the combined exposures to multiple fixtures, the concentration values (median 10^{-2} to 10^{3} *L. pneumophila* per L) overlap with some of the current guidance values (10^{2} to 10^{5} per L, with species not specified), although the guidance values would be on the higher end of the simulated ranges. Specifically, median critical concentrations calculated in the current models ranged from ~10^{-2} to ~10^{0} CFU per L and ~10^{1} to ~10^{3} CFU per L for infection and CSI dose response models, respectively. Due to the high value of a *Legionella* DALY (0.97), the conversion between annual infection or CSI risks and DALY infection or DALY CSI risks is approximately a factor of 100. All guidance values reviewed were above infection dose response model estimates, and the corresponding risk values for various concentrations specified in the guidance can be interpreted directly from Figure 3 or Supplemental Table S1. Most guidance values were consistent with, or had some management actions associated with, a CSI aggregate exposure model critical median concentration of <10^{3} CFU per L, but only the French Ministry of Health had a value for at-risk patients of ~ <10 CFU per L.[57] As the lower calculated values using an infection dose response model (10^{-2} to 10^{-1} CFU per L) may be below the detection limits of some culture-based assays, in routine practice it is likely to be more practical to apply the results of the CSI models. However, for immune-compromised or healthcare facility-associated populations, the infection model results might be more applicable which would correspond to <14.2 CFU per mL for a DALY metric and <1380 CFU per mL for an annual infection risk metric. Small differences were observed between target concentrations for conventional and water efficient fixtures, and therefore having two sets of distinct criteria by fixture type may be less practical than simply choosing the more conservative of the two. If choosing the more conservative median value from the CSI model for nonhealthcare water systems with a 10^{-6} DALY pppy target, then the recommended critical concentration would then be 12.3 CFU per L arithmetic mean (across multiple fixtures and/or over time). Choosing a 10^{-6} DALY/(365*f), which is essentially a 10^{-6} DALY pppy target corrected for comparison on a per exposure basis for a general population, single sample critical concentrations at each fixture would be 1060 CFU per L (faucets), 8840 CFU per L (toilets), and 14.4 CFU per L (showers).

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The risk criteria used in a previous *Legionella* QMRA by Schoen and Ashbolt[32] (per-exposure risk, for a single exposure) are different than the risk targets used here (10^{-4} annual infection risk and 10^{-6} DALY pppy, assuming exposures over a year period). Additionally, a key difference between the current model and the Schoen and Ashbolt model is the use of a factor of (Concentration of aerosols in size bin i) × (Volume of aerosols in size bin i) compared to the use of partitioning coefficient (P), respectively. A partitioning coefficient was used only for the faucet model in the current analysis due to lack of aerosol size-specific information. Partitioning coefficients tend to result in higher risk estimates compared to other methods of estimating *Legionella* risks;[29] therefore, the current model parametrization would theoretically result in a higher tolerated concentration than in the former model on a per-exposure basis. It is emphasized here that the results from the current model are not directly comparable to previously simulated critical values for *L. pneumophila* in premise plumbing.[32] If a hypothetical direct comparison were made, then critical bulk water concentrations from the current study are clearly lower compared to those previously derived for a single showering event (3.5×10^6 to 3.5×10^8 CFU per L), calculated using a target deposited dose of 1−100 CFU.[32] If making a direct comparison to data from dose response model curves, then a dose of 1 CFU would correspond to a median target per-exposure risk ranging from 0.06 (infection dose response model) to 6.20×10^{-5} (CSI dose response model) and a dose of 100 CFU would correspond to a median target risk ranging from ∼1 (infection dose response model) to 6.20×10^{-3} (CSI dose response model).

The critical concentration values presented in this analysis should be interpreted with caution, as risks were simulated for a variety of scenarios due to imperfect knowledge regarding spatial and temporal distribution of *L. pneumophila* within premise plumbing systems. The models do not include confounding factors such as differences in biofilm buildup and release, or overall potential to grow higher numbers of *L. pneumophila* based on microbial ecology factors such as the presence of amoeba. Quantitative rates for these parameters remain a research gap for *Legionella* spp. risk assessment.

Although data available for *Legionella* spp. in hot and cold water indicates higher concentrations in hot water, most fixtures will have mixing valves between a hot water heater and the tap. The temperature profile with respect to time was not considered in the current model, but would be valuable to include in an approach for evaluating the impact of various plumbing configurations on risks. Additionally, the temperature of the cold water line in some cases may still reach warm temperatures, and therefore there could still be growth in the cold water lines.

The current approach assumes that all culturable *L. pneumophila* measured are capable of causing infection. However, culture-based methods will not quantify all viable *Legionella* spp. The critical concentrations calculated in this analysis are for culturable *L. pneumophila*, as the dose response model for *L. pneumophila* derived using culture-based measurements was used. If measurements are made using qPCR, additional calculations may be needed for translating gene copies to viable microorganisms; this point has been highlighted by multiple authors[58,59] and although attempts have been made to make such a conversion,[60,61] additional comparative data sets would be valuable for deriving statistical models for such purposes. Accordingly, qPCR numbers should not be readily applied to the current model without harmonizing units of gene copies and colony forming units, and great care should be taken if molecular methods are used because the model is based on culturable *L. pneumophila*. Additionally, other species of *Legionella* are known to cause infection,[27] and therefore a critical concentration based solely upon *L. pneumophila* may not fully encapsulate risks due to exposure to other *Legionella* spp.

Very limited information exists regarding the partitioning, fate, and transport of *L. pneumophila* or other *Legionella* spp. bacteria in aerosol over both short-range and long-range spatial scales. Exposure to aerosols could potentially happen over longer times, depending on air exchange rates and activity patterns of occupants which were not considered herein. Furthermore, aerosol size distribution information from common water fixtures is sparse, but can potentially have a large impact on risk estimates. While shower exposures clearly drive *Legionella* risks in the indoor environment and therefore warrant the most attention, several gaps are noted for aerosol size information for other fixtures. For toilets, the height at which the aerosol size profile is measured may have an impact on risks, and additional measurements of toilet aerosols at higher heights (42 mm) above the toilet seat[33,34] compared to measurements by Johnson, Lynch, Marshall, Mead, and Hirst[42] have demonstrated that fewer aerosols were measured at what may be considered a more appropriate breathing height. In the current toilet model, the measurements for efficient and conventional toilets were made in the same experimental apparatus. However, in our previous assessment, differences in these parameters did not have as large of an influence on final simulated risks compared to other parameters.[31] For faucets, extremely limited information was available and highlights a research gap for further study. Due to very limited aerosolization information from literature data, the impact of flow rates, relative humidity, solute concentrations, and other factors on *Legionella* spp. in aerosols is not well characterized and was therefore not included in the model. A simplifying assumption was made in the current model that changes in relative humidity and drying of aerosols would not significantly impact the concentrations of *L. pneumophila* in aerosol over the time scales of exposure considered (<10 min). Experiments conducted by O'Toole et al.[33,34] were performed under conditions thought to be representative of typical fixture usage, however the shower experiments were run until surrounding air in the shower enclosure was saturated, which would have been supportive of aerosol generation and persistence. While water efficient fixtures were observed to produce fewer aerosols and result in lower risks compared to conventional fixtures, the models in the current analysis assumed the same average concentration at each fixture type. In practice, green fixtures may ultimately produce higher risk if higher concentrations are present in green buildings, therefore, this is an area where additional investigation is necessary to identify other factors contributing to *Legionella* risk in various building types.

Exposure parameters were simulated for a typical indoor premise plumbing environment, without consideration of the distribution of susceptible populations or varying activity patterns; for example, a hospital patient may use a shower less frequently than a healthy individual. In particular, shower durations might vary by subpopulation,[41] however, this information was not available for immune-compromised or

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hospitalized groups. The value for shower duration chosen for use in the current model[39] is consistent with other values reported in the literature[41] and was chosen for making comparisons among faucet, shower, and toilet usage as DeOreo et al.[39] assessed usage patterns for all three fixtures in the same report. An attempt was made to address susceptible populations by using two dose response models for infection and CSI. The interpretation of these two dose response models can be for different health endpoints (the former being representative of a subclinical infection or case of Pontiac Fever, while the latter might be considered representative of a case of Legionnaires' Disease requiring medical care). This distinction could also be interpreted in terms of subpopulations, with perhaps disease in an immune-compromised population would be represented by the infection endpoint, and disease in a healthy population represented by the CSI endpoint. Additional exploration of the plausibility of each of these inferences is needed, but requires information regarding exposure dose and subpopulation-specific attack rates for a given outbreak, for example, in order to make such a determination. It is often challenging to obtain all of this information for an outbreak.

Additionally, it is likely that throughout the course of a day, a person would come into contact from multiple fixtures, at multiple locations. Combinations of different fixtures could produce varying risk profiles and warrant further investigation. Especially within water efficient buildings, exposure to other water types such as harvested rainwater, gray water, or other recycled water is feasible and was not considered. Nuances in terms of these differences were not accounted for in the current model but could be addressed in a more detailed model of *Legionella* exposure in the premise plumbing environment.

Within different building types, it is possible that the types of fixtures could vary; for example in health-care facilities, aerosol generating medical equipment and ice machines might be more important drivers of risk compared to faucets or toilets. The aspiration pathway was not considered in the current analysis but may also play a more important role in a health-care setting. Outdoor exposures to aerosol generating devices such as cooling towers were not incorporated as the present model addresses premise plumbing water systems; however, a similar exercise could be performed for such an exposure. Finally, while *L. pneumophila* is a driving concern for building water quality, other water quality concerns should be concurrently weighed such as risks from other opportunistic premise plumbing pathogens (*Mycobacterium* spp., *Pseudomonas* spp., *Naegleria* spp., and others) as well as disinfection byproducts and metals, for example. Incorporating decision frameworks for such a purpose could be beneficial to extending this approach to a more comprehensive suite of health-related risks and to provide additional information regarding the relative merits of various water quality management options.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.8b03000.

Tabulated critical concentrations of culturable L. pneumophila associated with various risk benchmarks (PDF)

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Notes

The authors declare no competing financial interest.

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