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Modeling the survival kinetics of *Salmonella* in tree nuts for use in risk assessment

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ABSTRACT

Salmonella has been shown to survive in tree nuts over long periods of time. This survival capacity and its variability are key elements for risk assessment of *Salmonella* in tree nuts. The aim of this study was to develop a mathematical model to predict survival of *Salmonella* in tree nuts at ambient storage temperatures that considers variability and uncertainty separately and can easily be incorporated into a risk assessment model. Data on *Salmonella* survival on raw almonds, pecans, pistachios and walnuts were collected from the peer reviewed literature. The Weibull model was chosen as the baseline model and various fixed effect and mixed effect models were fit to the data. The best model identified through statistical analysis testing was then used to develop a hierarchical Bayesian model. *Salmonella* in tree nuts showed slow declines at temperatures ranging from 21 °C to 24 °C. A high degree of variability in survival was observed across tree nut studies reported in the literature. Statistical analysis results indicated that the best applicable model was a mixed effect model that included a fixed and random variation of δ per tree nut (which is the time it takes for the first $\log_{10}$ reduction) and a fixed variation of ρ per tree nut (parameter which defines the shape of the curve). Higher estimated survival rates (δ) were obtained for *Salmonella* on pistachios, followed in decreasing order by pecans, almonds and walnuts. The posterior distributions obtained from Bayesian inference were used to estimate the variability in the $\log_{10}$ decrease levels in survival for each tree nut, and the uncertainty of these estimates. These modeled uncertainty and variability distributions of the estimates can be used to obtain a complete exposure assessment of *Salmonella* in tree nuts when including time–temperature parameters for storage and consumption data. The statistical approach presented in this study may be applied to any studies that aim to develop predictive models to be implemented in a probabilistic exposure assessment or a quantitative microbial risk assessment.

1. Introduction

Tree nuts have been recognized for their potential contribution to foodborne illnesses (Frelka and Harris, 2014). *Salmonella* in particular, appears to be of concern in tree nuts, as it has been associated with foodborne outbreaks and recalls. From 2010 to January 2015, there have been four outbreaks linked to *Salmonella* in tree nuts in the U.S., one in 2014 involving *S.* Braenderup in almond butter, two in 2013: *S.* Stanley in raw cashew "cheese" and *S.* Senftenberg in roasted pistachios, and one in 2011 involving *S.* Enteritidis in pine nuts (Harris et al., 2015). There have also been numerous recalls indicating reoccurring microbial food safety issues due to *Salmonella* presence in walnuts, macadamia nuts, pecans, cashews, almonds, pistachios, pine nuts and hazelnuts (Palumbo et al., 2015). To assist development of a quantitative assessment of the risk of human salmonellosis associated with the consumption of tree nuts, the U.S. Food and Drug Administration requested data and models on survival of *Salmonella* in tree nuts through Federal Register Notice FDA-2013-N-0747-0001. Available and published *Salmonella* survival data were submitted in response to this notice. This includes raw data from the studies of Abd et al. (2012) (almonds), Beuchat and Mann (2010) (pecans), Blessington et al. (2012) (walnuts), Blessington et al. (2013a) (almonds and walnuts), Blessington et al. (2013b) (walnuts), Brar et al. (2015) (pecans), Kimber et al. (2012) (almonds and pistachios), and Uesugi et al. (2006) (almonds) (which was submitted via personal communication with the authors). In all of these studies, *Salmonella* was shown to be able to survive for weeks, months and even years. Survival curves tend to show a relatively rapid initial decline, followed by slow or no measurable decline over a much longer period of time, i.e., long term persistence (Frelka and Harris, 2014). However, differences in the shape of the survival curves have been observed depending on the study, the substrate, and/or the environmental conditions under which the experiments take place. Several

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mathematical models, including the log-linear model (Bigelow and Esty, 1920), the Geeraerd-tail model (Geeraerd et al., 2000), the Weibull model (Mafart et al., 2002; Peleg and Cole, 1998) and the biphasic linear model (Cerf, 1977) have been shown to appropriately describe the survival kinetics of *Salmonella* in low-a_w foods (Santillana Farakos et al., 2013). Of the aforementioned models, the Weibull model (Mafart et al., 2002; Peleg and Cole, 1998) has been shown to provide the best description of *Salmonella* survival kinetics in low a_w foods (Abd et al., 2012; Ma et al., 2009; Mattick et al., 2001; Santillana Farakos et al., 2013).

Survival kinetics of *Salmonella* in low-a_w foods should be considered in quantitative risk assessment. Two survival models have been developed for use in a quantitative risk assessment of *Salmonella* in almonds (Danyluk et al., 2006; Lambertini et al., 2012). Both of these models assume log-linear declines of *Salmonella* in almonds and do not incorporate variability and uncertainty. Survival curves of *Salmonella* in tree nuts have been shown to be non-linear (Abd et al., 2012; Beuchat and Mann, 2010; Blessington et al., 2012; Blessington et al., 2013a; Brar et al., 2015; Kimber et al., 2012; Uesugi et al., 2006). Moreover, the precision level of a quantitative risk assessment of *Salmonella* in tree nuts may be defined by the ability of the risk model to reflect and evaluate variability and uncertainty separately (Delignette-Muller et al., 2006; Nauta, 2000; Pouillot et al., 2003). Uncertainty represents the lack of perfect knowledge of the system, notably of the parameter value, while variability represents heterogeneity in the population exposure or response (Nauta, 2000). Additional *Salmonella* survival data would be helpful for a variety of tree nuts (e.g. pistachios where the data are available only from a single reference) and data are lacking for several others (e.g. chestnuts, cashews, macadamia nuts, pine nuts and hazelnuts). There is a great variability in the published literature of *Salmonella* survival for the same tree nut tested at similar temperatures. Survival of *Salmonella* in low-a_w foods has been shown to be affected by many factors including temperature, a_w, food composition, strain, and the experimental conditions of the study (Santillana Farakos et al., 2014). Models able to predict the dynamics of *Salmonella* survival in tree nuts that consider variability and uncertainty will be useful in assessing the risk of human salmonellosis from consumption of these products.

The objective of the current study was to develop a mathematical model to predict survival of *Salmonella* in tree nuts at typical storage temperatures (21–24 °C) that incorporated variability and uncertainty separately and could be readily incorporated into a quantitative risk assessment model. In this manuscript, we specifically focus on presenting the methodology to derive such a model.

2. Materials and methods

2.1. Data selection

The peer reviewed literature was searched for data on *Salmonella* survival in tree nuts using search engines PubMed, Web of Science and Google Scholar with keywords such as water activity, low moisture, temperature, tree nuts, nuts, almonds, pecans, walnuts, pistachios, modeling, kinetics, inactivation, and survival. The studies to be included in the analysis were restricted to those in which *Salmonella* survival was determined at ambient lab temperature (20 to 25 °C) which is a common storage temperature for tree nuts. Within these studies, data points with contamination levels lower than 1 cfu/unit were discarded (assuming the minimum amount of *Salmonella* per unit to be 1 cell). Curves showing increased cell population numbers with time were not included because, as no growth is expected at the usual a_w of these nuts, these curves represent specific conditions that are not expected to fall in the process modeled here. These need/will be included in a follow-up risk assessment however. Independent Weibull models were fit to each replicate and those representing outliers presumably the result of experimental error were not included. Out of the eight studies for which we received data, seven studies contained data that met the inclusion criteria: Abd et al. (2012); Beuchat and Mann (2010); Blessington et al. (2013a,b), Brar et al. (2015); Kimber et al. (2012) and Uesugi et al. (2006). Substrates included in the analysis comprise almonds, pecans, pistachios and walnuts. The recovery medium in the selected studies was either tryptic soy or bismuth sulfite based agar with different supplements. For the purpose of this analysis, the recovery medium was classified as either TSA if it was tryptic soy based or BSA if it was bismuth sulfite based, without taking into account the supplements added to the agar base. Each survival curve obtained from the seven studies is represented as a unique replicate for our analysis. A total of 111 replicates were included. The largest number of replicates (74 replicates) were available for *Salmonella* survival in almonds, followed in decreasing order by walnuts (24 replicates), pecans (7 replicates) and pistachios (6 replicates) (see supplementary data).

2.2. Modeling strategy

The classic approach (frequentist) to model selection is a tradeoff between the measure of model fit (e.g. deviance statistic) and the measure of complexity (e.g. number of parameters) (Spiegelhalter et al., 2002). The use of empirical posterior distributions obtained from a Monte-Carlo Markov Chain (MCMC) within a Bayesian inference framework has been previously described as being the most appropriate approach to develop mathematical models that incorporate variability and uncertainty separately (Delignette-Muller et al., 2006; Pouillot et al., 2003; Rigaux et al., 2013; Teunis et al., 2010). However, model selection using a Bayesian inference framework is complex and time consuming. In this study, we developed a strategy for modeling survival of *Salmonella* in tree nuts that combines the strengths of the frequentist and the Bayesian frameworks. We propose using a frequentist framework (testing both fixed and mixed effect models) to find the best applicable model to describe the kinetics of *Salmonella* survival in tree nuts and using a Bayesian framework to estimate the distribution of the survival parameters of the model to be implemented in a risk assessment.

2.3. Choosing the best applicable model

In the extensive data collection and analysis of *Salmonella* survival in low-a_w foods by Santillana Farakos et al. (2013), the Weibull survival model (Peleg and Cole, 1998) was shown to be the best applicable model to describe survival kinetics at temperatures ranging from 21 to 80 °C and a_w levels below 0.6. *Salmonella* in low-a_w foods typically show survival curves with a fast initial linear decline followed by slow decline with a non-zero asymptotic tail. The model is written as:

$$\log_{10}(N_t) = \log_{10}(N_0) - (t/\delta)^{\rho} \quad (1)$$

where N_0 is the concentration at time 0, N_t is the concentration at time t, δ is the time to the first $\log_{10}$ reduction, and ρ is a fitting parameter that defines the shape of the curve. The Weibull model can describe $\log_{10}$ linear ($\rho = 1$), concave ($\rho < 1$) and convex ($\rho > 1$) curves and assumes the resistance to stress of the population follows a Weibull distribution (Coroller et al., 2006; Peleg and Cole, 1998). Although the Weibull model is of an empirical nature, a link can be made with physiological effects: $\rho < 1$ indicates that the remaining cells have the ability to adapt to the applied stress, whereas $\rho > 1$ indicates that the remaining cells become increasingly damaged (Peleg and Cole, 1998; van Boekel, 2002).

The Weibull survival model (Peleg and Cole, 1998) was thus chosen for further analyses.

2.3.1. Fixed effect models

Using classical nonlinear least squares regression, fixed effect models were used to determine the level of variability in the parameters δ and ρ of the Weibull model. The parameters δ and ρ can be the same

for all curves, can vary by substrate (almond, pecan, pistachio, or walnut) and/or can vary by replicate (with a total of 111 replicates). The sequences of models tested are provided in Table 1. Two concurrent fixed effect models were compared using an *F*-test (95% confidence level) when one model was nested in the other one. When the two concurrent models were not nested, they were compared on the basis of the Bayesian Information Criteria (BIC) (Schwarz, 1978). BIC was chosen as the model evaluation metric because it has a larger penalty term for models with a higher number of parameters as compared to the Akaike Information Criterion (AIC). This allows for better discrimination of models when testing models with a very high number of parameters. When no *F*-test was available, a model with a lower BIC was preferred.

2.3.2. Mixed (random) effect models

When using a frequentist framework, an alternative method to considering variability is the use of mixed effect models. Mixed effects models include fixed and random factors. A fixed factor considers the level of interest constant (e.g. per tree nut or per replicate), while a random factor considers the levels under study to be a sample from a population. The use of mixed effect models versus fixed effect models allows the user to generalize the results to a population of studies that were not included in the analysis (Jaloustre et al., 2012) as would be needed in a quantitative risk assessment. In addition to fixed effect models, various mixed effect models were fit to the data based on the results obtained from the fixed effect models. These mixed effect models are shown in Table 1. Models were compared using a likelihood-ratio test ($p < 0.05$) if nested. When the models were not nested, the BIC was used to determine the best applicable model.

Table 1
Type of model, model number, model parameters, parameter variability and model to be compared with for the various fixed effect and mixed effect models based on the Weibull survival model (Peleg and Cole, 1998).

Type	Model #	Parameter	Level of variability[c]	Compare with model #[d]
Fixed effect	1	δ[a], ρ[b]	None	
	2	δ	Per substrate	1
		ρ	None	
	3	δ	None	1
		ρ	Per substrate	
	4	δ, ρ	Per substrate	1, 2 and 3
	5	δ	Per replicate	1 and 2
		ρ	None	
	6	δ	None	1 and 3
		ρ	Per replicate	
	7	δ	Per replicate	1, 2, 3, 4 and 5
		ρ	Per substrate	
	8	δ	Per substrate	1, 2, 3, 4 and 6
		ρ	Per replicate	
	9	δ, ρ	Per replicate	1, 2, 3, 4, 5, 6, 7 and 8
Mixed effect	10	δ	Random per replicate	1
		ρ	None	
	11	δ	Random per replicate, fixed per substrate	1 and 10
		ρ	None	
	12	δ	Random per replicate, fixed per substrate	1 and 11
		ρ	Fixed per substrate	
	13	δ	Random per replicate, fixed per substrate	1 and 11
		ρ	Random per replicate	
	14	δ, ρ	Random per replicate, fixed per substrate	1, 12 and 13

– not applicable.
[a] Time (in weeks) to the first $\log_{10}$ reduction.
[b] Parameter defining the shape of the curve.
[c] Specifies whether the parameter does not vary, varies by substrate and/or varies by replicate.
[d] Model(s) provided in this column are nested in the model of this row.

2.3.3. Hierarchical Bayesian model

The best model identified through systematic evaluation of fits for each of the proposed models (described above) was used in a hierarchical Bayesian model that included uninformative priors. Prior distributions reflect previous knowledge on the parameters of interest (Gilks et al., 1996). An inference step then produces a posterior distribution by conditioning the prior parameter distributions to observed data (Gilks et al., 1996). The difference between the prior and posterior distributions can be interpreted as an update on previous knowledge provided by observed data (Gilks et al., 1996). A direct calculation of posterior distributions can be very challenging. The MCMC technique is a very powerful tool that generates chains of simulated values for parameters with a sampling algorithm that converges to the posterior distribution of interest (Gilks et al., 1996). The analyses in this study were performed in line with that described in previous studies (Delignette-Muller et al., 2006; Pouillot et al., 2003). Briefly, three Markov Chains of 100,000 values were used and the first 10,000 values of each chain were discarded in order to reach convergence of the posterior distribution. One value was recorded every 10 iterations until 10,000 values were recorded for each of the three chains to avoid inter-chain correlation. Convergence was checked using Gelman and Rubin's convergence diagnostic with a value under 1.1 used as a sign of convergence (Gelman and Rubin, 1992).

All frequentist models were developed and fit using R (R Core Team, Vienna, Austria, 2016). The nls function (package stats) was used to fit the fixed effect models and the nlme function (package nlme) was used to fit the mixed effect models. Contrasts were tested considering multiple comparisons (package multcomp). JAGS, through the rJAGS R library, was used for the Bayesian model fitting (Plummer, 2013). N_0 was considered a nuisance parameter specific to each fit. The media (TSA and BSA) were considered a factor of influence to the fit through N_0 and captured by the variability in δ for a given substrate. Codes are available in the supplementary data.

3. Results and discussion

3.1. Survival data

In this analysis, the survival data for *Salmonella* on almonds, pecans, pistachios and walnuts at temperatures ranging from 21 to 24 °C as reported by each of the studies included in this analysis are presented in Figs. 1 through 4, respectively. The kinetics represented by these data were generally characterized by a relatively fast initial population decline during the first few weeks of storage, followed by long term persistence with slow or no decline over time. The data in Figs. 1 through 4 represent the set of data from a given reference, regardless of replicate

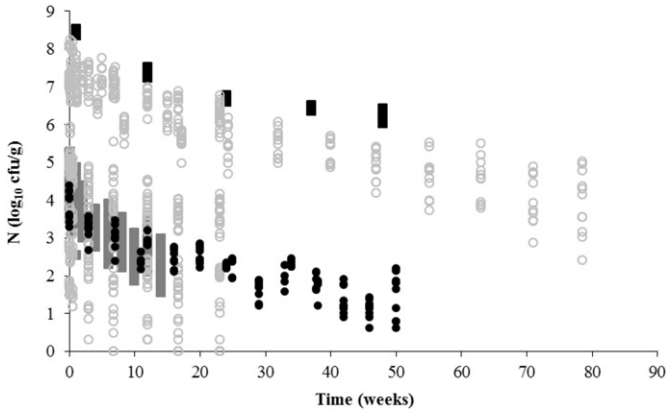

Fig. 1. *Salmonella* spp. survival at 21 °C < T < 24 °C on almonds as reported in (■) Blessington et al. (2013a), (■) Abd et al. (2012), (○) Uesugi et al. (2006) and (●) Kimber et al. (2012).

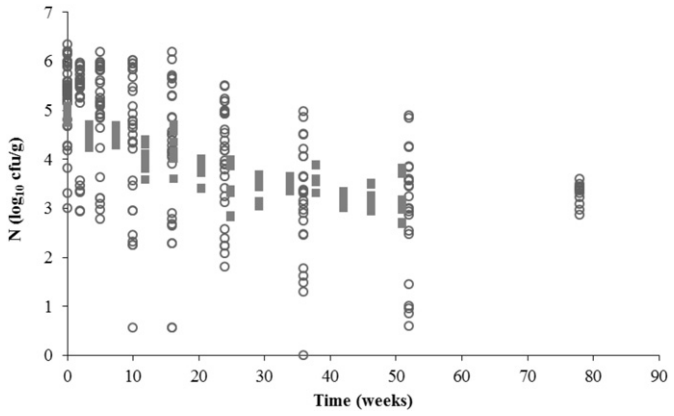

Fig. 2. *Salmonella* spp. survival at 21 °C < T < 24 °C on pecans as reported in (○) Beuchat and Mann (2010) and (■) (Brar et al., 2015).

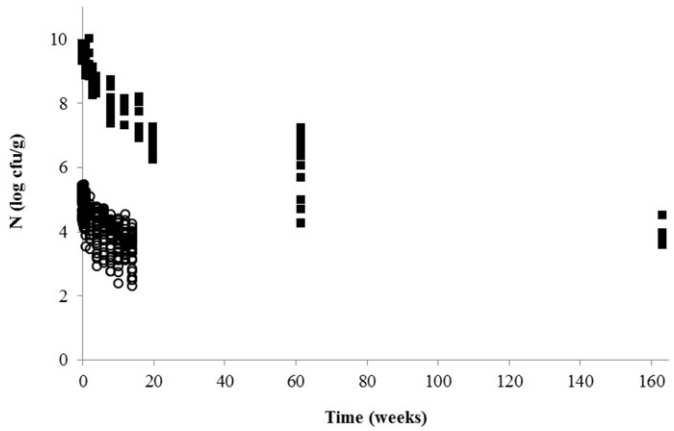

Fig. 4. *Salmonella* spp. survival at 21 °C < T < 24 °C on walnuts as reported by (○) Blessington et al. (2013a) and (■) Blessington et al. (2013b).

or media. Almonds averaged declines of approximately 1 — $\log_{10}$ CFU after 12 weeks and 2 — $\log_{10}$ CFU after 48 weeks of storage for storage at ambient temperature (21–24 °C) and a_w levels ranging from 0.4 to 0.5 (Fig. 1). After 48 weeks of storage, no significant further reductions were observed. In the case of pecans, the data from Beuchat and Mann (2010) at 21 °C and a_w levels ranging from 0.4 to 0.6 showed 1 — $\log_{10}$ CFU reduction after 10 weeks of storage, followed by slower reduction in population levels for the remaining weeks up to a total of 78 weeks. *Salmonella* survival on pecans by Brar et al. (2015) at 22 °C and a moisture content of approximately 3% (which is equivalent to a a_w of 0.4 (Beuchat, 1978)) showed slightly different results as compared to that from Beuchat and Mann (2010). *Salmonella* populations on pecans took 20 weeks for the first $\log_{10}$ reduction and declined by 2 — $\log_{10}$ CFU after 52 weeks of storage (Brar et al., 2015). In line with the results seen on almonds and pecans, *Salmonella* on pistachios at 24 °C and a_w levels of around 0.4 (Fig. 3) was very persistent, with an average 15 weeks of storage time to achieve the first $\log_{10}$ reduction followed by an additional 1 — $\log_{10}$ reduction during the remaining weeks up to 52 (Kimber et al., 2012). Similar to the other tree nuts, data from Blessington et al. (2013a) on survival of *Salmonella* on walnut kernels at 23 °C and a_w levels ranging from 0.4 to 0.5 (Fig. 4) shows the first $\log_{10}$ reduction at around 5 weeks of storage followed by little or no additional decline over time (Blessington et al., 2013a,b). These faster initial declines observed in the pecan data collected by Beuchat and Mann (2010) compared to Brar et al. (2015) and in the *Salmonella* survival on in-shell walnuts (Blessington et al., 2013b) as compared to walnut kernels (Blessington et al., 2013a) could be attributed to the fact that these studies did not provide time for a relative humidity equilibration period after the 24 h post inoculation drying time. Overall, differences of

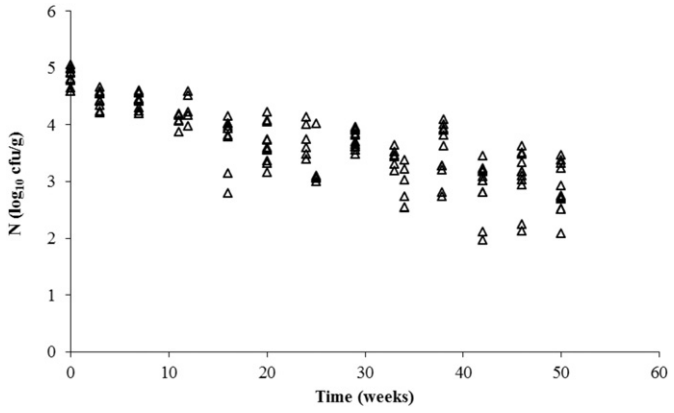

Fig. 3. *Salmonella* spp. survival at 21 °C < T < 24 °C on pistachios in $\log_{10}$ cfu/g as reported by Kimber et al. (2012).

Salmonella resistance between nut types were already described for pistachios and almonds (Kimber et al., 2012) or X ray resistance almonds and walnuts (Jeong et al., 2012). While differences in water activity or tree nut composition clearly have a role, the exact reason of these differences is not yet fully described.

Statistical analysis of these data, as described in the Materials and methods section, shows a high degree of variation in *Salmonella* survival numbers at the same time point for the same tree nut at similar temperatures as illustrated by the parameter estimates for δ in the fixed and mixed effects models (Tables 3 and 4). The differences in survival for the various replicates likely reflect the net differences in the observed survival arising from the combination of differences in relative humidity, physical characteristics of the various varieties of tree nuts, strain, study design, and inoculum preparation method (e.g. growth in broth versus growth on agar, wet versus dry inoculation). The shape parameter, ρ, showed to be variable per tree nut (Table 3, model 12), but the use of a distribution of ρ within the same tree nut did not improve the model significantly (Table 3, model 14).

3.2. Fixed effect models

Given the variability of the dataset, the first step in determining the best applicable model was to fit the Weibull fixed effect models (Table 1, models 1 through 9) to the dataset to obtain the variability levels specific to parameters δ and ρ (Peleg and Cole, 1998). Model fit statistics for the Weibull fixed effect models are presented in Table 2. As seen in this table, models fit the data better when some level of variability per tree nut is incorporated in parameters δ and/or ρ. The BIC scores and *F*-test results showed that model 2 (δ varying per substrate), model 3 (ρ varying per substrate) and model 4 (δ and ρ varying per substrate) were a significantly better fit to the data when compared to model 1 (no variability included). Additionally, model 4 provided a statistically significant better fit when compared to model 3 and model 2. These results emphasize the importance of a predictive model of survival of *Salmonella* in tree nuts including variability per tree nut in the parameter describing the time to the first $\log_{10}$ reduction (δ) and the parameter which defines the shape of the curve (ρ).

Increased predictive value in the model is observed when there is a δ value for each replicate rather than just for each tree nut (model 5). This is reflected in the statistical analysis results of the *F*-test used comparing model 2 with model 5 (Table 2). It is noteworthy to mention that models 5, 6, 7, 8 and 9 in Table 2 have a much higher number of parameters compared to models 1, 2, 3 and 4. The number of parameters in the model is taken into account in the calculated BIC values and in the *F*-test. Models 5, 6, 7, 8 and 9 in Table 2 showed consistently higher BIC values compared to models 1, 2, 3, and 4. The quality of fit of the model was significantly improved when, in addition to having a δ value for each

Table 2
Statistical analysis results of the various Weibull fixed effect models.

Model	Parameter estimate $\delta \pm$ se[a]					Parameter estimate $\rho \pm$ se[b]					BIC[c]	*F*-test results
	All	Almond	Pecan	Pistachio	Walnut	All	Almond	Pecan	Pistachio	Walnut		
1	6.8 ± 0.36					0.50 ± 0.011					4045	–
2		6.0 ± 0.32	10.0 ± 0.68	13.0 ± 1.6	5.3 ± 0.38	0.51 ± 0.011					3919	Better than model 1 ($p < 10^{-4}$)
3	6.4 ± 0.33						0.52 ± 0.013	0.44 ± 0.013	0.39 ± 0.022	0.53 ± 0.012	3971	Better than model 1 ($p < 10^{-4}$)
4		6.0 ± 0.41	12.7 ± 1.4	18.6 ± 3.9	4.4 ± 0.47		0.51 ± 0.015	0.58 ± 0.036	0.66 ± 0.098	0.48 ± 0.016	3929	Better than model 2 ($p = 0.006$) Better than model 3 ($p < 10^{-4}$)
5	Multiple[d]					0.51 ± 0.013					4116	Better than model 2 ($p < 10^{-4}$)
6		5.1 ± 0.28				Multiple					4330	Better than model 3 ($p < 10^{-4}$)
7	Multiple						0.53 ± 0.022	0.61 ± 0.033	0.68 ± 0.089	0.42 ± 0.018	4092	Better than model 5 ($p < 10^{-4}$)
8		4.2 ± 0.33	12.5 ± 1.3	18.3 ± 3.3	3.4 ± 0.47	Multiple					4237	Better than model 6 ($p < 10^{-4}$)
9	Multiple					Multiple					4820	Not Better than model 7 ($p > 0.05$) Better than model 8 ($p < 10^{-4}$)

– Not applicable.
[a] Time (in weeks) to the first $\log_{10}$ reduction $\pm$ standard error.
[b] Parameter defining the shape of the curve $\pm$ standard error.
[c] Bayesian Information Criterion.
[d] 111 replicates each with a different parameter average and standard error (data not shown).

replicate (model 5), the model included a ρ value that varied for each tree nut (model 7). Indeed, Table 2 shows model 7 has a lower BIC score compared to model 5. Adding variability per replicate rather than per tree nut for parameter ρ (model 9) resulted in a higher BIC score with no added predictive value to the model. A *F*-test indicates a much better fit of model 7 when compared to model 2 ($p < 10^{-15}$). All in all, the statistical analysis results of the fits using the fixed effect models suggested that a model incorporating variability of δ per replicate and a fixed ρ value per tree nut (model 7) is the best applicable model to describe the survival kinetics of *Salmonella* on almonds, pecans, pistachios and walnuts.

3.3. Mixed effect models

The fitting results with the mixed effects model tested in this study are presented in Table 3. Model 12 in Table 3 which considers a random variation of δ per tree nut (rather than a fixed parameter value for each tree nut) and a fixed value of ρ per tree nut, appears to be the best model compared to simpler (model 10 and model 11) and a more complex mixed effect model (model 14). Model 13 which also considers a random variation of δ per tree nut and a random variation of ρ has increased predictive potential when compared to model 11 but is not better than a more complex model like model 14 (Table 3). In fact, statistical analysis results for significant difference testing in the time to the first $\log_{10}$ reduction (δ) as estimated for the various tree nuts, after consideration of the multiple comparisons, showed that there are significant differences in the δ values when comparing almonds versus pecans ($p < 0.001$), almonds versus pistachios ($p = 0.003$), almonds versus walnuts ($p = 0.040$), pecans versus walnuts ($p < 0.001$) and pistachios versus walnuts ($p < 0.001$). There were no significant differences in the time to the first $\log_{10}$ reduction when comparing δ values for pecans versus pistachios ($p = 0.222$). Shape parameter values (ρ) were significantly different for almonds versus pecans ($p < 0.001$), almonds versus walnuts ($p = 0.03$), pecans versus walnuts ($p < 0.001$) and pistachios versus walnuts ($p = 0.04$). There were no significant differences in the shape parameter values for almonds versus pistachios and pecans versus pistachios ($p > 0.05$). These results are in line with the model testing results that showed increased predictability of the survival model when parameter δ is allowed to vary by tree nut but the value of ρ per tree nut is fixed.

Table 3
Statistical analysis results of the various Weibull mixed effect models.

Model	Parameter estimate $\delta \pm$ se[a]				Parameter estimate $\rho \pm$ se[b]				BIC[c]	*F*-test results
	Almond	Pecan	Pistachio	Walnut	Almond	Pecan	Pistachio	Walnut		
10	$6.2 \pm .39$ Sd[d]: 2.5				0.48 ± 0.011 No random variation				3729	Better than model 1 ($p < 10^{-4}$)
11	$5.9 \pm .39$ Sd: 2.1	9.9 ± 1.2	11.4 ± 1.6	5.1 ± 0.57	0.48 ± 0.011 No random variation				3721	Better than model 10 ($p < 10^{-4}$)
12	$6.0 \pm .48$ Sd: 2.2	13.6 ± 1.6	17.6 ± 3.4	3.9 ± 0.63	0.49 ± 0.017 No random variation	0.59 ± 0.032	0.65 ± 0.085	0.42 ± 0.018	3714	Better than model 11 ($p < 10^{-4}$)
13	$4.72 \pm .35$ Sd: 1.1	11.9 ± 1.2	11.6 ± 2.0	3.7 ± 0.49	0.45 ± 0.014 Sd: 0.070				3722	Better than model 11 ($p < 10^{-4}$)
14	$4.7 \pm .37$ Sd: 1.2	12.9 ± 1.3	16.1 ± 3.2	3.4 ± 0.49	0.44 ± 0.017 Sd: 0.056	0.57 ± 0.040	0.61 ± 0.081	0.40 ± 0.023	3729	Not better than model 12 ($p > 0.05$) Better than model 13 ($p < 10^{-4}$)

[a] Time (in weeks) to the first $\log_{10}$ reduction $\pm$ standard error.
[b] Parameter defining the shape of the curve $\pm$ standard error.
[c] Bayesian Information Criterion.
[d] Standard deviation of the random effect.

Table 4
Descriptive statistics of the empirical posterior distributions from the Bayesian inference model describing *Salmonella* survival at 21 °C < T < 24 °C in almonds, pecans, pistachios and walnuts.

Variables	Mean	SD	Quantile				
			2.5%	25%	50%	75%	97.5%
δ^{a}_{almond}	7.7	0.8	6.0	7.2	7.7	8.2	9.2
δ^{a}_{pecan}	15.6	2.1	11.4	14.1	15.5	16.9	20.0
$\delta^{a}_{pistachio}$	20.2	3.7	13.1	17.7	20.1	22.7	27.4
δ^{a}_{walnut}	3.2	1.4	0.4	2.2	3.2	4.1	5.8
ρ^{b}_{almond}	0.53	0.02	0.49	0.52	0.53	0.54	0.57
ρ^{b}_{pecan}	0.61	0.03	0.55	0.59	0.61	0.63	0.67
$\rho^{b}_{pistachio}$	0.69	0.09	0.53	0.63	0.68	0.75	0.91
ρ^{b}_{walnut}	0.43	0.02	0.40	0.42	0.43	0.44	0.47
σ^{c}_{δ}	0.37	0.01	0.36	0.37	0.37	0.38	0.38
σ^{d}	4.05	0.61	3.02	3.62	3.99	4.43	5.36

See Eq. (4) for the specification of the parameters.
[a] Time (in weeks) to the first log10 reduction.
[b] Parameter defining the shape of the curve.
[c] Standard deviation of the variability distribution of δ.
[d] Standard error of the residual.

The BIC scores for the mixed effect models were lower than those for the fixed effect models (Tables 3 and 4, respectively). This is because in the mixed effect models one parameter is estimated to account for replicate variability versus using a parameter for each of the replicates in a fixed effect model approach. More specifically, the fixed effect model 7 (Table 1) can be written as Eq. (2). In this fixed effect model (Eq. (2)), there is no constraint regarding the distribution of the δ_r.

$$\log_{10}(N_t) = \log_{10}(N_{0,e}) - (t/\delta_r)^{\rho_s} + \varepsilon \quad (2)$$

where N_0, N_t, t, δ, and ρ are defined as above, e represents the experimental trials ($e = 1, \ldots,194$), r in δ represents the replicate ($r = 1,\ldots,111$), s represent the substrate and ε is an error term that is assumed to follow a normal distribution $\varepsilon \sim Normal(0,\sigma)$.

The mixed effect model 12 would be written as Eq. (3). Models such as Eq. (3) are built under two assumptions. The first assumption is the random effect follows a normal distribution. The second assumption is the random effect is uncorrelated with the explanatory variable (δ_s and/or p_s).

$$\log_{10}(N_t) = \log_{10}(N_{0,e}) - (t/(\delta_s + r_\delta))^{\rho_s} + \varepsilon \quad (3)$$

where N_0, N_t, t, δ, ρ, e, and ε are defined as above with s in δ_s and p_s representing the tree nut, almonds, pecans, pistachios or walnuts, and with the random effect on r_δ following $Normal(0,\sigma_\delta)$.

The mixed effect model considers only one estimated parameter (σ_δ) to account for the variability of δ where the fixed effect model uses 111 parameters. This explains the observed lower BIC scores in the mixed effect models.

A strong correlation between δ and ρ parameters is expected in Weibull inactivation models, (Coroller et al., 2006; van Boekel, 2002). We obtained strong positive correlation coefficients of 0.70, 0.69, 0.87 and 0.51 between δ and ρ for almond, pecan, pistachio and walnut, respectively.

3.4. Bayesian inference

Transferring correlation between parameters and parameter uncertainty from frequentist inference processes to a quantitative risk assessment is not direct, while essential (Smith et al., 1992). Bootstrap sampling can be used (Pouillot and Delignette-Muller, 2010). Another option is to use Bayesian hierarchical modeling (Delignette-Muller et al., 2006; Pouillot et al., 2003). The advantage of using Bayesian inference, as compared to the mixed effect model approach, is that Bayesian modeling makes it easier to estimate the uncertainty of each parameter from the posterior distribution obtained (Jaloustre et al., 2012) and to incorporate it in a subsequent risk assessment model. In fact, Bayesian inference has been used in previous meta-analyses when developing models to be used in risk assessment (Delignette-Muller et al., 2006; Pouillot et al., 2003). For the purpose of this study, a model analog to model 12 was developed in a Bayesian framework. This model is written as Eq. (4).

$$\begin{aligned} \log_{10}(N_{e,t}) &\sim Normal(\log_{10}(N_{0,e}) - (t/(\delta_r))^{\rho_s}, \sigma) \\ \delta_r &\sim Normal(\delta_s, \sigma_\delta), \quad \text{with } \delta_r > 0 \end{aligned} \quad (4)$$

with the following uninformative priors

$$\begin{aligned} \log_{10}(N_{0,e}) &\sim Normal(6, 10) \\ \rho_s &\sim Uniform(0, 2) \\ \delta_s &\sim Uniform(0, 40) \\ \sigma^{-2} &\sim Uniform(0, 10) \\ \sigma_\delta^{-2} &\sim Uniform(0, 10) \end{aligned}$$

where N_0, N_t, t, δ_r, δ_s, ρ, and e defined as above, $Normal(a, b)$ stands for a normal distribution with mean a and standard deviation b and $Uniform(a,b)$ stands for a uniform distribution with minimum a and maximum b.

The residuals from the Bayesian model are estimated from the empirical mean of the posterior distribution of the expected value associated with each observation. The residuals appear to be randomly distributed around the value zero and do not increase as the $\log_{10}$ survival count for *Salmonella* increases (see supplemental material). This observation suggests a good fit of the model to the data.

The descriptive statistics of the empirical posterior distributions of the survival parameters for *Salmonella* survival in tree nuts as obtained with the Bayesian model are provided in Table 4. Higher estimated survival rates (δ) in weeks are obtained for *Salmonella* on pistachios (20.2 ± 3.7), followed in decreasing order by pecans (15.6 ± 2.1), almonds (7.7 ± 0.8) and walnuts (3.2 ± 1.4). These estimations for parameters δ and ρ (parameters which define the shape of the curve) are slightly different from the estimations given by model 12 (mixed effect model, Table 3). As seen in Table 4 and compared to Table 3, the estimates from the Bayesian inference model for both δ and ρ are generally larger, with a larger variation than when using the mixed effect model approach. These estimates differ because *i*) in the Bayesian hierarchical model, the distribution of δ_r is not only assumed to be normal, as in mixed effect models, but is actually modeled using a normal distribution; and *ii*) the prior distribution (even when chosen as uninformative) may impact the estimates. As seen by the results in Table 4, the variability of the δ parameter (as indicated by the standard deviation) is highest for pistachios ($\delta_{pistachios}$) followed in decreasing order by pecans (δ_{pecans}) and walnuts ($\delta_{walnuts}$), all being considerably higher than for almonds ($\delta_{almonds}$). This precision reflects the number of replicates available for each tree nut.

3.5. Implementation of the derived survival model in a risk assessment model

In Table 5, the $\log_{10}$ decrease in survival for *Salmonella* (as obtained through the posterior distributions from the Bayesian inference framework) are presented for each tree nut, including an uncertainty and a variability dimension. The uncertainty dimension was simulated by sampling values in the MCMC chain. For a given uncertainty iteration (e.g. u), one needs to consider δ_u, $sd_{\delta u}$, and p_u (δ_u, $sd_{\delta u}$ and p_u are issued from the same MCMC iteration to preserve the correlation between those parameters). The variability dimension was calculated by selecting a value δ using $\delta_{u,v} \sim \text{Normal}(\delta_u, sd_{\delta u})$. The $\log_{10}$ decrease L ($\log_{10}$ cfu/g) was calculated as $(t/_{u,v})^{\rho_u}$ for any time t. Moreover, in Fig. 5, the median estimate of the $\log_{10}$ reduction levels are presented as a function of time for almonds, pecans, pistachios and walnuts. As

Table 5
Log_{10} decrease values for almonds, pecans, pistachios and walnuts at various storage times between 1 and 52 weeks at temperatures ranging from 21–24 °C including the variability and uncertainty dimensions.

Substrate	Time (weeks)	Uncertainty dimension	Variability dimension						
			Mean	sd	2.5%	25%	50%	75%	97.5%
Almonds	1	Median	−0.40	0.29	−0.89	−0.41	−0.33	−0.29	−0.23
		Mean	−0.40	0.37	−0.92	−0.42	−0.34	−0.29	−0.23
		2.5%	−0.49	0.13	−1.36	−0.50	−0.39	−0.33	−0.27
		97.5%	−0.33	1.03	−0.62	−0.35	−0.29	−0.25	−0.20
	4	Median	−0.83	0.60	−1.87	−0.86	−0.70	−0.60	−0.49
		Mean	−0.84	0.77	−1.92	−0.87	−0.70	−0.60	−0.49
		2.5%	−1.00	0.28	−2.80	−1.01	−0.79	−0.67	−0.55
		97.5%	−0.72	2.16	−1.32	−0.76	−0.63	−0.54	−0.43
	12	Median	−1.48	1.08	−3.36	−1.54	−1.25	−1.08	−0.87
		Mean	−1.50	1.38	−3.44	−1.55	−1.25	−1.08	−0.87
		2.5%	−1.78	0.50	−5.01	−1.78	−1.37	−1.17	−0.96
		97.5%	−1.31	3.86	−2.37	−1.39	−1.15	−0.98	−0.78
	52	Median	−3.23	2.35	−7.33	−3.36	−2.73	−2.34	−1.90
		Mean	−3.27	3.02	−7.49	−3.39	−2.73	−2.34	−1.90
		2.5%	−3.85	1.09	−10.87	−3.85	−2.96	−2.52	−2.07
		97.5%	−2.88	8.50	−5.25	−3.05	−2.53	−2.16	−1.73
Pecans	1	Median	−0.20	0.04	−0.29	−0.21	−0.19	−0.17	−0.15
		Mean	−0.20	0.05	−0.30	−0.22	−0.19	−0.17	−0.15
		2.5%	−0.28	0.02	−0.51	−0.29	−0.25	−0.23	−0.19
		97.5%	−0.15	0.18	−0.20	−0.16	−0.14	−0.13	−0.11
	4	Median	−0.46	0.09	−0.67	−0.49	−0.44	−0.40	−0.34
		Mean	−0.46	0.13	−0.70	−0.50	−0.44	−0.40	−0.34
		2.5%	−0.61	0.05	−1.13	−0.64	−0.55	−0.49	−0.42
		97.5%	−0.36	0.41	−0.49	−0.39	−0.35	−0.32	−0.28
	12	Median	−0.89	0.18	−1.30	−0.96	−0.86	−0.78	−0.67
		Mean	−0.90	0.24	−1.37	−0.97	−0.86	−0.78	−0.67
		2.5%	−1.14	0.10	−2.16	−1.21	−1.03	−0.91	−0.78
		97.5%	−0.74	0.80	−1.00	−0.80	−0.72	−0.66	−0.57
	52	Median	−2.18	0.43	−3.18	−2.34	−2.09	−1.90	−1.63
		Mean	−2.21	0.59	−3.35	−2.37	−2.10	−1.90	−1.63
		2.5%	−2.70	0.25	−5.15	−2.87	−2.44	−2.16	−1.83
		97.5%	−1.88	1.91	−2.52	−2.02	−1.83	−1.67	−1.44
Pistachios	1	Median	−0.13	0.02	−0.18	−0.14	−0.13	−0.12	−0.10
		Mean	−0.14	0.03	−0.20	−0.15	−0.13	−0.12	−0.11
		2.5%	−0.26	0.01	−0.41	−0.28	−0.25	−0.23	−0.20
		97.5%	−0.05	0.09	−0.07	−0.06	−0.05	−0.05	−0.04
	4	Median	−0.34	0.05	−0.47	−0.37	−0.33	−0.30	−0.26
		Mean	−0.35	0.06	−0.49	−0.37	−0.34	−0.31	−0.27
		2.5%	−0.56	0.02	−0.89	−0.60	−0.53	−0.48	−0.41
		97.5%	−0.19	0.20	−0.25	−0.20	−0.18	−0.17	−0.14
	12	Median	−0.72	0.11	−0.98	−0.77	−0.70	−0.65	−0.56
		Mean	−0.73	0.13	−1.03	−0.78	−0.71	−0.65	−0.56
		2.5%	−1.01	0.06	−1.66	−1.08	−0.96	−0.87	−0.75
		97.5%	−0.50	0.38	−0.65	−0.54	−0.49	−0.45	−0.38
	52	Median	−1.97	0.30	−2.69	−2.11	−1.91	−1.76	−1.53
		Mean	−1.99	0.36	−2.79	−2.14	−1.93	−1.76	−1.53
		2.5%	−2.39	0.19	−4.03	−2.57	−2.25	−2.02	−1.74
		97.5%	−1.69	0.93	−2.16	−1.80	−1.66	−1.53	−1.33
Walnuts	1	Median	−0.66	0.50	−1.74	−0.70	−0.54	−0.44	−0.35
		Mean	−0.66	0.56	−1.74	−0.70	−0.54	−0.44	−0.35
		2.5%	−0.81	0.28	−2.33	−0.86	−0.63	−0.52	−0.40
		97.5%	−0.52	1.23	−1.16	−0.55	−0.44	−0.38	−0.30
	4	Median	−1.20	0.91	−3.14	−1.27	−0.97	−0.80	−0.64
		Mean	−1.20	1.01	−3.15	−1.27	−0.97	−0.81	−0.64
		2.5%	−1.45	0.52	−4.24	−1.52	−1.13	−0.91	−0.71
		97.5%	−0.97	2.25	−2.15	−1.02	−0.82	−0.70	−0.56
	12	Median	−1.92	1.45	−5.03	−2.02	−1.55	−1.29	−1.02
		Mean	−1.93	1.62	−5.05	−2.03	−1.56	−1.29	−1.02
		2.5%	−2.31	0.84	−6.83	−2.44	−1.79	−1.45	−1.13
		97.5%	−1.57	3.62	−3.47	−1.66	−1.34	−1.14	−0.91
	52	Median	−3.61	2.72	−9.41	−3.81	−2.92	−2.42	−1.92
		Mean	−3.62	3.05	−9.49	−3.82	−2.92	−2.42	−1.92
		2.5%	−4.38	1.57	−13.03	−4.62	−3.37	−2.72	−2.11
		97.5%	−2.95	6.83	−6.51	−3.12	−2.52	−2.15	−1.72

seen in Table 6 and Fig. 5, higher estimated survival rates (δ) in weeks are obtained for *Salmonella* on pistachios, followed in decreasing order by pecans, almonds and walnuts. These results are in line with those seen from the estimates of δ with model 12 (Table 3), which show that *Salmonella* in pistachios have the highest resistance, followed in decreasing order by *Salmonella* in pecans, almonds and walnuts. The results shown in Fig. 5 visually indicate that almonds and walnuts have similar survival kinetics and that these are different from those found for pistachios and pecans (where almonds and walnuts show a lower resistance). These results are in line with the results from significant different testing in the times to the first $\log_{10}$ reduction (δ) as estimated for the various tree nuts and discussed above.

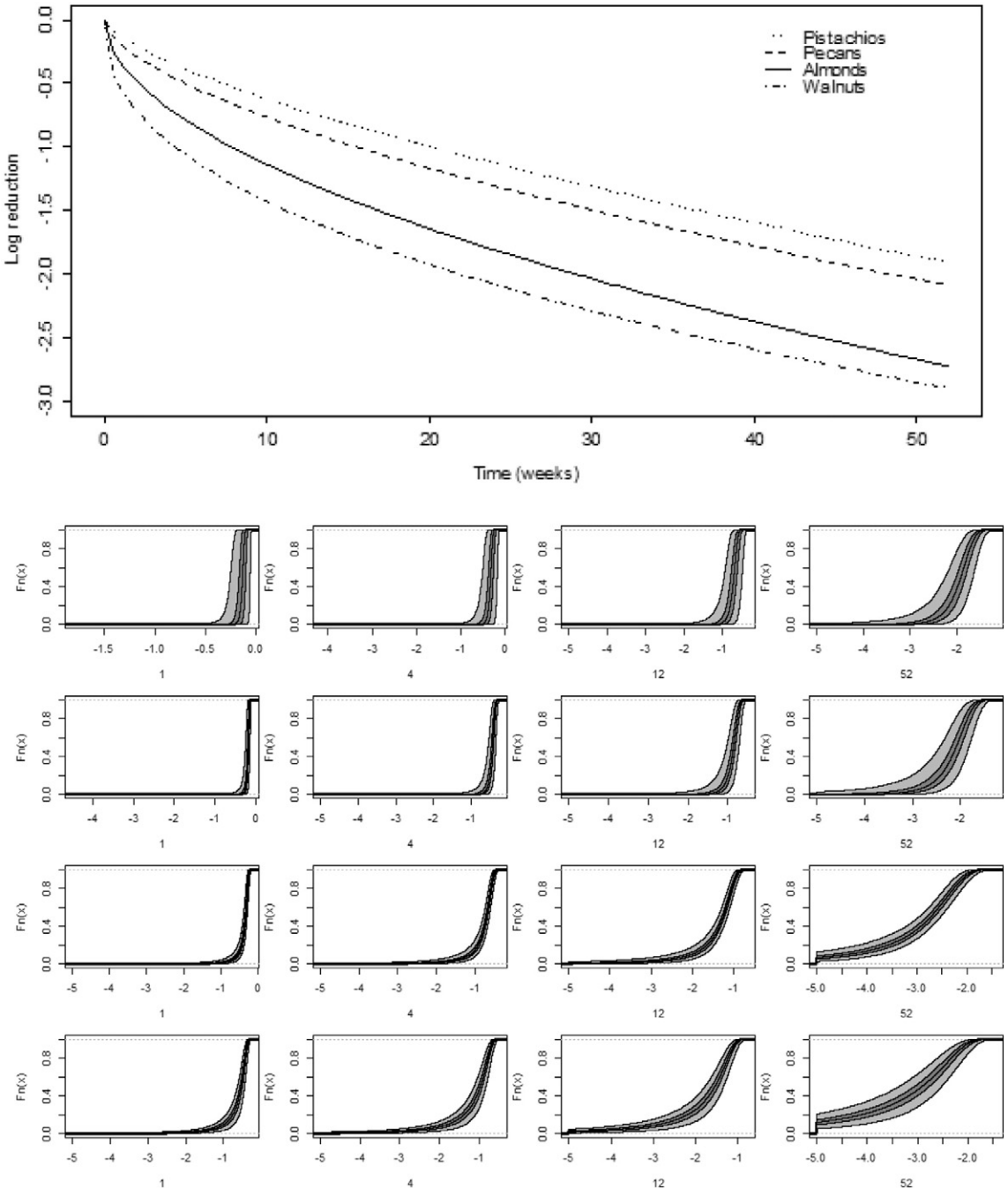

Fig. 5. Top: median estimate of the $\log_{10}$ reduction as a function of time for pistachios, pecans, almonds and walnuts where vertical lines represent 0, 1, 4, 12 and 52 weeks. Bottom: second-order Monte-Carlo output of the $\log_{10}$ reductions at 1, 4, 12 and 52 weeks (from left to right) for pistachios, pecans, almonds and walnuts (from top to bottom), including the upper and lower values (in light gray) and the 2.5th and 97.5th percentiles representing the uncertainty ranges of the estimated value (in dark gray).

Also shown in Fig. 5 are the outputs of the second order Monte-Carlo simulation of the $\log_{10}$ reduction at 1, 4, 12 and 52 weeks for all tree nuts, including the upper and lower values (in light gray) and the 2.5th and 97.5th percentiles representing the uncertainty ranges of the estimated value (in dark gray). These modeled uncertainty and variability distributions of the estimates (as shown in Table 5) can be used to obtain a complete exposure assessment of *Salmonella* in tree nuts when including a time–temperature model and consumption data.

Risk assessments for *Salmonella* in almonds have used log-linear inactivation models with a point estimate (-0.25 $\log_{10}$ cfu/month as reported by Danyluk et al. (2006), which is -0.06 $\log_{10}$ cfu/week) or a variability distribution of the $\log_{10}$ decrease (Normal(-0.0078388, 0.00178) per day as reported in Lambertini et al. (2012), which is Normal(-0.055, 0.012) per week). In these studies, the $\log_{10}$ reductions for 7 trials were pooled and a normal distribution was fitted to the 7 corresponding $\log_{10}$ linear slopes. Our results suggest that the log-linear model is not the best model to describe such data, as reflected by the very low (significantly lower than 1) values of ρ (parameter which defines the shape of the curve) that were estimated. More refined approaches using frequentist mixed effect models or Bayesian hierarchical models are now recommended for such meta-analyses (Diao et al., 2014; Jaloustre et al., 2012; Pouillot et al., 2003; Silva et al., 2015). Our protocol evaluated what would be the best model to describe *Salmonella* survival data in tree nuts among Weibull type models. Other models describing bacterial survival and inactivation are available (Geeraerd et al., 2005) and can be used with this same approach.

The data used for this study come from a limited number of publications and the impact of *Salmonella* strain, laboratory protocols, experimental conditions beyond temperature and water activity and what time (after inoculation) the authors considered to be time 0 were not separately accounted for and varied among studies. A more refined experimental design, in which similar strains would be used in various laboratories under defined conditions, would be needed to test for differences in results when using data from the different studies and environmental conditions. Currently, a confounding effect of the strain and laboratory conditions is present in the data. The results obtained with this study apply to the survival of *Salmonella* spp. in almonds, pecans, pistachios and walnuts at temperatures ranging from 21 to 24 °C. The model could be further extended to include other tree nuts and incorporate a secondary model whenever more data are available for other temperatures and environmental factors such as a_w.

4. Conclusions

In this study, a framework is presented to derive a *Salmonella* survival model that can be easily implemented in a risk assessment model for tree nuts and that is able to separate uncertainty and variability. The evaluation and separation of uncertainty and variability within risk assessments is a recurring recommendation in national and international guidelines such as CAC (1999); FAO/WHO (2002) and FAO/WHO (2003) (Delignette-Muller et al., 2006). However, few predictive microbiology model inference frameworks allow this separation. The methodology presented herein employs a frequentist framework to select the best model structure followed by a Bayesian framework to obtain a multivariate posterior distribution that can be directly implemented in a probabilistic risk assessment model. This systematic approach to modeling could be used for various types of models, including growth, inactivation and transfer.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijfoodmicro.2016.03.014.

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