Estimators of annual probability of infection for quantitative microbial risk assessment

N. Karavarsamis and A. J. Hamilton

ABSTRACT

Four estimators of annual infection probability were compared pertinent to Quantitative Microbial Risk Analysis (QMRA). A stochastic model, the Gold Standard, was used as the benchmark. It is a product of independent daily infection probabilities which in turn are based on daily doses. An alternative and commonly-used estimator, here referred to as the Naïve, assumes a single daily infection probability from a single value of daily dose. The typical use of this estimator in stochastic QMRA involves the generation of a distribution of annual infection probabilities, but since each of these is based on a single realisation of the dose distribution, the resultant annual infection probability distribution simply represents a set of inaccurate estimates. While the medians of both distributions were within an order of magnitude for our test scenario, the 95th percentiles, which are sometimes used in QMRA as conservative estimates of risk, differed by around one order of magnitude. The other two estimators examined, the Geometric and Arithmetic, were closely related to the Naïve and use the same equation, and both proved to be poor estimators. Lastly, this paper proposes a simple adjustment to the Gold Standard equation accommodating periodic infection probabilities when the daily infection probabilities are unknown.

Key words | dose-response, estimator, infection risk, probabilistic model, stochastic, uncertainty

N. Karavarsamis (corresponding author)
Department of Mathematics and Statistics,
Faculty of Science,
The University of Melbourne,
Parkville Victoria 3052,
Australia
Tel.: +61 3 8344 5550
Fax: +61 3 8344 4599;
E-mail: *nkarav@unimelb.edu.au*

A. J. Hamilton
Department of Resource Management and Geography,
Melbourne School of Land and Environment,
The University of Melbourne,
500 Yarra Boulevard,
Richmond, Victoria 3121,
Australia

INTRODUCTION

In general there are two ways of estimating annual probability of infection (annual infection risk) associated with environmental exposure to pathogens. First, direct observation through epidemiological studies can be used to establish an association between observable and known, or suspected, risk factors and the incidence or prevalence of the disease in question. A limitation of this approach is that confounding factors, i.e. influences on observed infection rates other than the assumed risk factors, can be difficult to control for. Also, from a practical perspective, risks often need to be estimated prior to engaging in the activity. For example, health and environmental authorities responsible for a proposed wastewater irrigation scheme would usually need to determine pathogen infection risks prior to its commission (Hamilton *et al.* 2007). Furthermore, epidemiological studies are typically specific to the scenario under investigation, and usually cannot be readily transferred to other situations where exposure pathways differ. These limitations, as well as the expense of conducting epidemiological studies, have driven the development of the second approach to determining infection probability, namely, quantitative microbial risk assessment (QMRA) (Haas *et al.* 1999); and it is in this context that infection probability estimation will be considered here.

QMRA uses prior knowledge about the circumstances that influence risk to construct a probabilistic model. It allows for estimating risk under infinite scenarios, although the assumption that the model accurately describes risk pathways must always be borne in mind. Nonetheless, QMRA is becoming an increasingly important tool for

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health authorities, and it is propounded in several major health guideline documents pertaining to water-borne pathogens (e.g. drinking water: WHO 2004; wastewater irrigation: USEPA & USAID 2004; NRMMC *et al.* 2006; WHO 2006; recreational waters: WHO 2003) and to food-safety in general (WHO & FAO 2006). It has also been widely used by researchers to estimate pathogen risks associated with meats (Nauta 2002, 2005; Nauta *et al.* 2005), drinking water (Teunis *et al.* 1997; Barbeau *et al.* 2000; Haas 2000), and wastewater-irrigated vegetables (reviewed by Hamilton *et al.* 2007).

QMRA is a four-step process comprising (i) hazard identification, (ii) exposure assessment, (iii) dose–response modelling, and (iv) risk characterization (Haas *et al.* 1999). Hazard identification simply involves determining the pathogens of concern, exposure assessment comprises defining the exposure pathway so the dose of the pathogens a person is exposed to can be determined, dose–response modelling defines the probability of infection as a function of this dose, and the final step, risk characterisation, brings all this together to arrive at an estimate of the probability of an adverse outcome, typically infection. The first two steps are clearly specific to the scenario at hand. Several dose-response models have been developed but two, the exponential and the beta-Poisson, are by far the most commonly used. The exponential has been widely employed to characterise infectivity of protozoan pathogens, such as *Cryptospordium parvum* and *Giardia intestinalis* (formerly *G. lamblia*), as well as several viruses; and the beta-Poisson has mostly been applied to bacterial pathogens but also to rotavirus (Haas *et al.* 1999). The exact beta-Poisson model, as derived by Furumoto & Mickey (1967), is rarely used, owing to its intractability, but their approximated version has seen broad application (see Haas *et al.* 1999; WHO 2006).

An important component of the risk characterisation step involves calculating total infection probability from estimates of infection probability per exposure event. The currency of total infection probability is typically annual probability of infection, with a probability of $\leq 10^{-4}$ often being used as an acceptable level of risk (USEPA 1989; Macler & Regli 1993), and an exposure event is usually defined in terms of daily exposure. Surprisingly little attention has been given to ways of estimating annual infection probability (annual infection risk) from daily probabilities. This paper explores the theoretical validity of four annual risk estimators and compares their performances through application to an example QMRA model.

Methods and description of estimators

Daily infection probability

To study the behaviour of the different annual probability estimators a distribution of daily infection probability, p, first had to be generated. The scenario chosen was enteric virus infection probability associated with consuming broccoli that had been spray irrigated with non-disinfected wastewater that had undergone secondary treatment (Hamilton *et al.* 2006*b*). The exposure model for determining daily dose, D, is given as

$$D = BMcV\mathrm{e}^{-(\lambda t)}, \tag{1}$$

where B = human body mass (Log Normal $[\mu = 61.429, \sigma = 13.362]$ kg); M = daily consumption of broccoli per capita per kg of body mass (0.102 g/kg/ca/d); c = enteric virus concentration in secondary effluent (Log Normal $[\mu = 0.15, \sigma = 0.63]$ colony forming units per mL); V = volume of water caught by 1 g of broccoli (Log Logistic $[\alpha = 4.246,\ \beta = 1.583 \times 10^{-2},\ \lambda = 1.085 \times 10^{-3}]$ mL g^{-1}); and $\mathrm{e}^{-(\lambda t)}$ is a first-order exponential decay model used to describe viral inactivation on the surface of the plant, where λ = kinetic decay constant (Normal $[\mu = 1.07, \sigma = 0.07]$) and t = the number of days elapsed since irrigation with wastewater (1 day). Justifications for the parameter values and distributions are given in Hamilton *et al.* (2006*b*). It is important to note here that the sole purpose of the exposure model was to construct a realistic dose distribution that could be used for our studies on the behaviour of the various annual risk estimators; there was no intent to infer infection risks associated with a particular wastewater irrigation system.

Having determined D, the approximate beta-Poisson dose-response model was used to estimate p as

$$p = 1 - \left(1 + \frac{D}{\beta}\right)^{-\alpha}, \tag{2}$$

where the values for the shape parameters α and β, 0.2531 and 0.4265 respectively, were obtained by Haas *et al.* (1999)

through maximum likelihood estimation (MLE) when applying the model to Ward *et al.* (1986) rotavirus infectivity trial on adult males. Owing to the dearth of such dose–response studies, this rotavirus model has frequently been used to represent enteric virus infection probability in general (van Ginneken & Oron 2000; Petterson *et al.* 2001, 2002; Hamilton *et al.* 2006*a*,*b*; Seidu *et al.* 2008).

Gold standard annual infection estimator P_{Gold}

The estimator to which all others will be compared will hereafter be referred to as the *Gold Standard* estimator. Described in detail elsewhere (Haas *et al.* 1999; Benke & Hamilton 2008), it assumes statistical independence of daily infection probabilities and is given as

$$P_{\mathrm{Gold}} = 1 - \prod_{k=1}^{365} (1 - p_k), \tag{3}$$

where p_k is the k^{th} daily infection probability. It demands 365 daily infection probabilities, which necessitates 365 estimates of daily dose, D_k, since a single p_k is derived from a single estimate of D_k. It follows that by requiring 365 estimates of daily infection probability, Equation (3) allows for and accounts for the variation in p_k.

Naïve annual infection estimator P_{Naive}

It is not always possible or practical to obtain an estimate of p_k for each day of the year. This has given rise to the use of a much simpler annual infection probability equation, here called the Naïve, which demands *one* estimate of daily infection probability only to obtain an estimate of annual infection probability. The Naïve estimator, P_{Naive}, is the most commonly used annual infection probability estimator in QMRA. It is a reduced version of the Gold Standard that naively assumes a *constant* daily probability of infection p for each day of the calendar year; thus

$$P_{\mathrm{Naive}} = 1 - (1 - p)^{365}, \tag{4}$$

where 365 is the number of days in a calendar year. In addition to the assumption of a constant daily probability of infection p (as per Equation (2)), P_{Naive} implicitly assumes a constant daily dose estimate D. That is, daily dose and, consequently, daily probability of infection are assumed to be the same for every day of the year, and therefore variability in these parameters is not accounted for. Equation (4) is often used in stochastic QMRAs in an attempt to account for variability (van Ginneken & Oron 2000; Hamilton *et al.* 2006*a*,*b*; WHO 2006; Mara *et al.* 2007; Seidu *et al.* 2008). The equation is implemented many times using simulation methods, with the value for p changing each time. This produces a distribution of naïve estimates of annual risk. Here the distribution of these inaccurate probabilities is compared to the Gold Standard distribution.

Geometric and Arithmetic annual infection estimators (P_{Geom} and P_{Arith})

In deterministic risk assessments the dose distribution is represented by a single value, a point-estimate. The Geometric, P_{Geom}, and Arithmetic, P_{Arith}, annual probability estimators attempt to aggregate the information of daily dose, D, into a mean of some form (Benke & Hamilton 2008). The objective is to capture the variability of daily dose into a summary statistic, used for calculating the daily infection probability, p, containing all the information about the variation in daily dose. This paper will explore the impact of this using the simulated results. The P_{Geom} and P_{Arith}, estimators are calculated in the same way as the Naïve estimator, P_{Naive} (Equation (4)), the only difference being that they use a mean daily dose $\bar{D}$, instead of a single realisation of daily dose D.

The Geometric estimator uses a geometric mean of the daily dose estimates, as the name suggests, whereby

$$\bar{D}_{\mathrm{Geom}} = 10^{\left(\left(\sum_{k=1}^{365} \log_{10} D_k\right)/365\right)}. \tag{5}$$

D_k is the estimated daily dose of the k^{th} day of the year, contributing to the Geometric mean daily dose $\bar{D}_{\mathrm{Geom}}$.

The Arithmetic estimator, on the other hand, relies on an arithmetic mean of the daily dose estimates and is described by

$$\bar{D}_{\mathrm{Arith}} = \left(\sum_{k}^{365} D_k\right)/365. \tag{6}$$

Subsequently, the dose–response Equation (Equation (2)) calculates an estimate of daily infection probability

respectively for each of the mean daily dose estimates. Lastly, the Naïve estimating Equation (4) produces an annual infection probability estimate for the Geometric and Arithmetic scenarios.

Adjusted Gold Standard annual infection estimator P^*_{Gold}

The Gold Standard is restricted to 365 daily infection probabilities. But it may not always be logistically feasible to obtain or determine daily doses. To this end proposed here is a new estimator that is an adjustment to the Gold Standard and is appropriate to use when daily dose samples are not available, i.e. when there are fewer than 365 dose estimates. Furthermore, as each dose estimate, D, produces a single daily infection probability, p, it follows that fewer than 365 dose estimates will result in fewer than 365 (daily) infection probabilities. In other words, there may be only weekly, monthly, seasonal or any other periodic infection probabilities, p^*, available. These will be called *Periodic Infection Probabilities* (p^*), rather than Daily Infection Probabilities (p), as there is no longer a distinct infection probability for each day of the year. This new estimator, the *Adjusted Gold Standard*, P^*_{Gold}, is defined as

$$P^*_{\text{Gold}} = 1 - \prod_{k=1}^{n_p} (1 - p^*_k)^{n_q}, \tag{7}$$

where p^*_k represents the kth periodic infection probability, n_p represents the number of periodic infection probabilities, p^*_k, in one year, and n_q represents the period over which the assumption of constant daily infection probability is extended.

The impact of various periodic infection probabilities on the stability of the adjusted Gold Standard estimator will be explored. This can be viewed as an exploration of the robustness of the adjusted Gold Standard estimator to sample size changes in the number of periodic infection probabilities, p^*_k, available for estimation. So, for example, if there were *weekly* infection probabilities available, a total of 52 (weekly) infection probabilities, and an estimate of annual infection probability would be calculated adopting the following Adjusted Annual infection probability equation:

$$P^*_{\text{Gold}}(52) = 1 - \prod_{k=1}^{52} (1 - p^*_k)^7 \tag{8}$$

where p^*_k, is the kth *weekly* infection probability of the year and is assumed constant within each week i.e. over the 7 day period.

Simulations and computations

The daily dose model (Equation (2)) was used to simulate sampling from the population of daily dose of infection. The Latin Hypercube Sampling (LHS) technique (Iman *et al.* 1980) was adopted to ensure that the tails of the input probability distributions were adequately sampled.

The daily dose population was generated using @Risk version 4.5.2, Professional edition (Palisade Corporation, Newfield, New York). This resulted in a population size of 98,500 daily dose values, D. This corresponds to a distribution of 270 estimates of the Gold Standard, and Geometric and Arithmetic estimators, a sample large enough (>100) for inferences/comparisons. It is important to note here that the Geometric and Arithmetic estimators have in the past been used in deterministic risk assessments only, and thus simulation has not been appropriate. However, here the purpose was to account for the variation attendant with sampling from a dose distribution, hence the need for simulation. Used was a simple random sample of 9,000 daily dose estimates from the simulated daily dose population for generating the distribution for the Naïve estimator. This resulted in 9,000 estimates of the Naïve estimator since a single daily dose observation, and thus a single daily infection probability, generates a single estimate of the Naïve annual infection probability estimator.

RESULTS

The distribution of estimated annual risks for P_{Naive} displayed a strong positive skewness, whereas the P_{Gold} distribution was symmetric (Figures 1 and 2, respectively). Notably, the 95th percentile of the Naïve (13.3%) even exceeds the upper range of the Gold Standard (max. = 5%) by more than double the risk. Therefore, the assumption of constant daily probability of infection was not satisfied here.

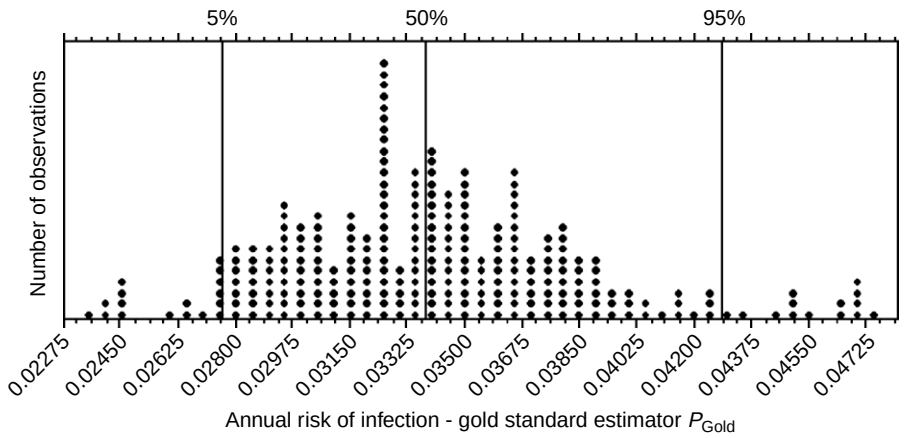

Figure 1 | Annual risk distribution - Gold standard estimator. Solid vertical lines represent the 5th and 95th percentile, and median (50th percentile).

The Arithmetic estimator's annual infection probability distribution compared well to the Gold Standard (Figure 3(b)). The shape and location parameters of the distributions were similar. The Geometric Estimator, on the other hand, resulted in an annual infection probability distribution of markedly different shape and location to the Gold Standard (Figure 3(a)).

Comparison of distributions fails to acknowledge the fact that the Arithmetic and Geometric estimators are not usually simulated, but rather a single value (point estimate) based on a sample of doses (here 365) is used. Therefore, it is more appropriate to examine the pair-wise comparisons between each (i.e. Geometric and Arithmetic) and the Gold Standard. Agreement with the Gold Standard was non-existent for both of the estimators (Figure 3). The Arithmetic estimator (Figure 3(b)) gives random estimates but a reasonable mean, and the Geometric estimator (Figure 3(a)) consistently underestimates the annual infection probability regardless of the magnitude of the actual annual infection probability.

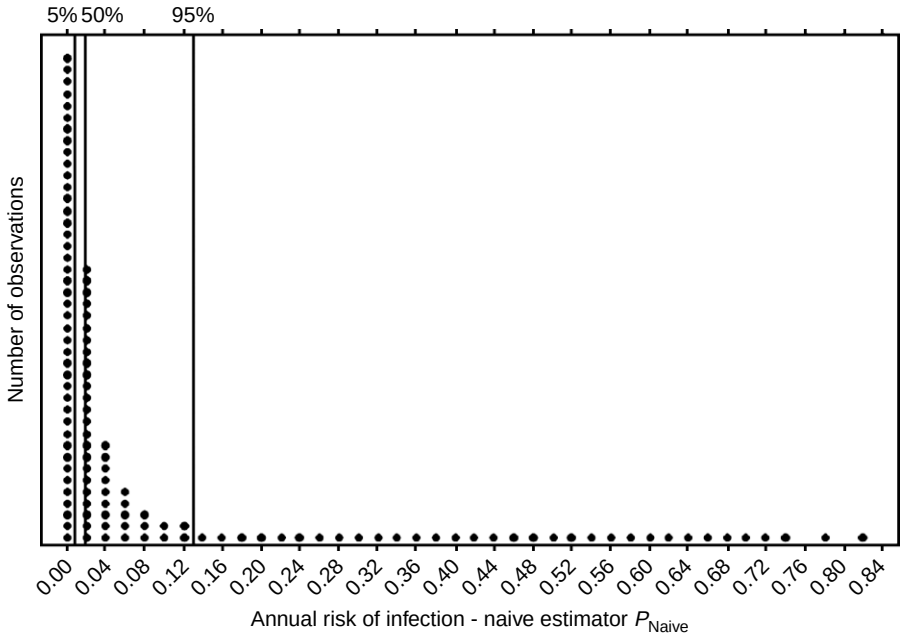

Figure 2 | Annual risk distribution – Naïve estimator. Each symbol represents up to 104 observations. Solid vertical lines represent the 5th and 95th percentile, and median (50th percentile).

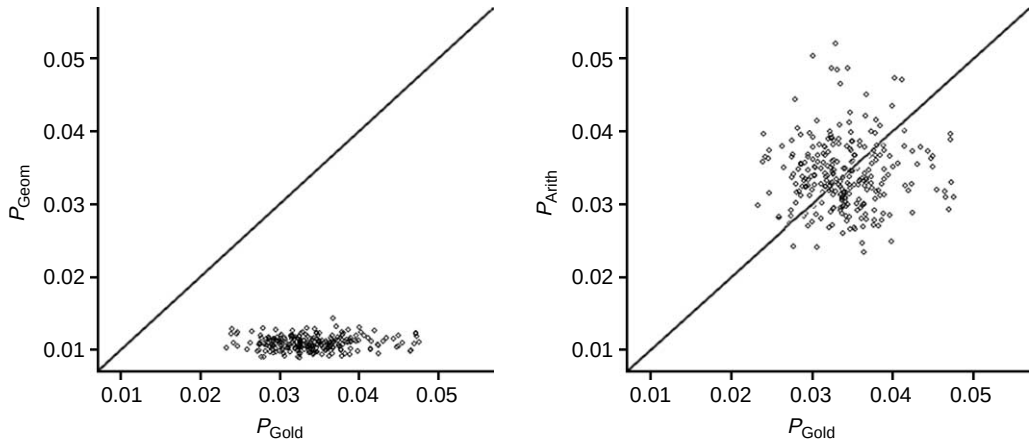

Figure 3 | Pair-wise comparisons of annual risk infection for the (a) Geometric estimator vs. the Gold standard and the (b) Arithmetic estimator vs. the Gold standard. The diagonal line represents perfect agreement between the estimators on the axes.

Distributions arising from the Adjusted Gold Standard decreased in skewness and standard deviation as the number of periodic infection probabilities, n_p, increased (Figure 4).

DISCUSSION

Many have attempted to account for uncertainty in the estimation of annual infection probability through generating a distribution of P_{Naive} s (e.g. van Ginneken & Oron 2000; Hamilton *et al.* 2006*a*,*b*; WHO 2006; Mara *et al.* 2007; Seidu *et al.* 2008). However, P_{Naive} assumes a constant infection probability, which itself is determined through a single realisation of the dose distribution. This realisation could be a poor representation of the dose distribution (*cf* a summary statistic, such as a measure of central tendency), and therefore will lead to an inaccurate estimate of annual risk. Repeating the process many times over will simply produce a distribution of inaccurate estimates of annual risk. Not only is each estimate based

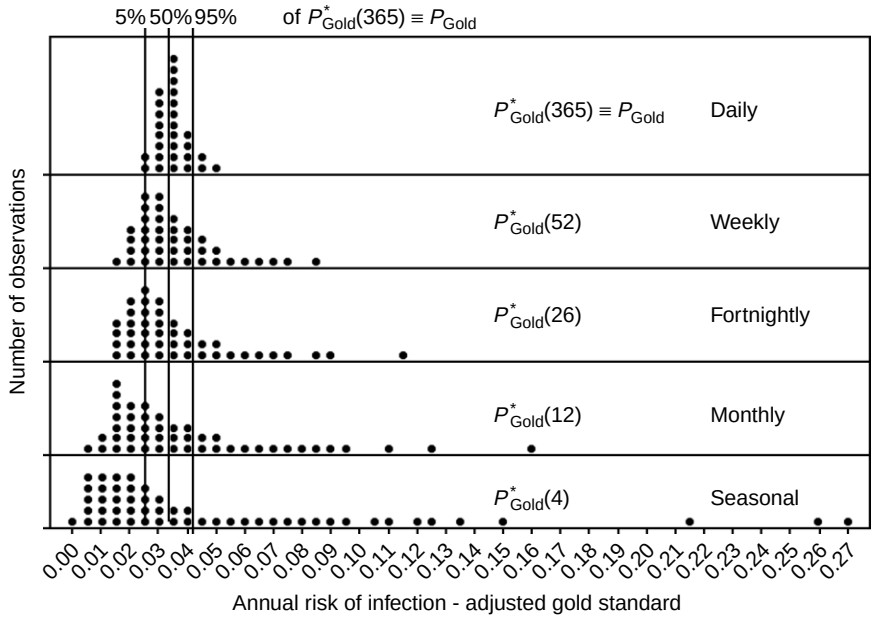

Figure 4 | Annual risk distributions for the Adjusted Gold standard estimator for various Periodic infection probabilities (daily, weekly, fortnightly, monthly, seasonal). Each symbol represents up to 11 observations. Solid vertical lines represent the 5th and 95th percentile, and median (50th percentile).

on the assumption of constant daily dose and infection probability, but the dose value used in any individual calculation is drawn at random from the dose population, and therefore the resultant value for P_{Naive} represents an inaccurate estimate of annual infection probability. This process can also be viewed in terms of pseudo-replication. For example, it is clearly more appropriate to use 365 realisations of dose, and hence daily infection probability, to calculate a single estimate of annual infection risk, P_{Gold}, than it is to assume that a single (daily) infection probability can be used to determine 365 separate estimates of 'annual' infection probability, P_{Naive}. Note that these 365 dose estimates can either be direct observations (e.g. from environmental samples taken on each day of the year) or, more likely, they can be generated through simulation of an exposure model. Demonstrated here was that for a realistic test scenario the distribution of P_{Naive} is markedly different from that of P_{Gold}, and consequently provides an inadequate representation of uncertainty of annual infection probability. Therefore recommended is that future stochastic QMRAs use the P_{Gold} estimator, which itself can be simulated many times to obtain a distribution.

The only similarity between the distributions of P_{Naive} and P_{Gold} was their arithmetic means (3.105 and 3.408%, respectively). Therefore, there would be little practical difference in the management of public health risk if the mean of the annual infection probability distribution were to be used to characterise risk. However, arithmetic means are inappropriate for comparing these distributions as the Naïve distribution is right-skewed, rendering the mean a biased measure of central tendency. The vastly different shapes of the distributions resulted in markedly different lower (Gold Standard 3%; Naïve 0.1%) and upper (Gold Standard 4%; Naïve 13%) 95% confidence limits, which are often used in QMRA to represent conservative estimates of the infection risk posed to a community (e.g. Tanaka *et al.* 1998; Hamilton *et al.* 2006*b*). In this instance, use of P_{Naive} would have resulted in an over-estimation of risk, relative to P_{Gold}, of around one order of magnitude.

Monte Carlo simulation tools are not always readily accessible or understandable to those wishing to conduct a QMRA. To this end, deterministic QMRAs may serve a purpose (NRMMC *et al.* 2006). A clear disadvantage of such models, of course, is that uncertainty is ignored. Nonetheless, given their ease of implementation, it is worthwhile considering their value. Explored here is annual risk estimation under the scenario of using a unique estimate of mean (arithmetic and geometric) daily dose for a calendar year. In this way the Geometric and Arithmetic estimators use 365 estimates of daily dose, D, for the inclusion into an estimate of annual mean daily dose, $\bar{D}$. This contrasts with the approach adopted by Benke & Hamilton (2008), where the *population* geometric and arithmetic means of the distribution of D were used for the deterministic model, and each of these annual risk estimates was compared to the distribution mean of a stochastic model based on the Gold Standard estimator. A limitation of that method is that it does not represent the realities of sampling to obtain a dose estimate. A dose mean determined from a sample could be very different from the dose mean of the respective/corresponding population distribution, particularly if the sample-size is small. Clearly, through taking environmental observations, the practitioner will only have a sample dose mean to work with, not the true population mean. In this study a sample of 365 doses was assumed, which could be presumed to represent an observation for each day of the year. This sample was taken many times, thus giving sampling distributions of the Geometric and Arithmetic estimators, instead of only a single estimate of annual risk from a deterministic model. While in terms of order of magnitude the mean of the $\bar{P}_{\text{Arith}}$ and $\bar{P}_{\text{Geom}}$ distribution coincided with the mean of the $\bar{P}_{\text{Gold}}$ distribution, the pair-wise comparisons, which test the hypothesis that a single point estimate correctly estimates the true population parameter of annual infection probability, demonstrated that neither offers a sound estimate of annual risk infection (Figure 3).

The performance of a new estimator, the Adjusted Gold Standard, was also assessed here. The estimator is flexible in that it allows for the assumption of constant infection probability to be held over a defined period. That is, it accommodates periodic dose values, whether they be weekly, fortnightly, monthly, or any other period. The accuracy and performance of the estimator diminished with decreasing number of periodic infection probabilities per year. Eventually, as the amount of daily dose information available reduces, so the number of daily dose values reduces to 1, and hence the annual risk equation reduces to

the Naïve estimator. The distributions also increased in symmetry with increasing number of periodic events (e.g. from daily to monthly, or other period), and this is consistent with the Central Limit Theorem. More work needs to be done in deriving an estimator that is robust and yet sufficient in producing accurate estimates of annual risk according to the amount of available information with respect to daily dose. One such way to progress this estimator could be to find out how the variability in daily infection probabilities affects the estimation of annual probability of infection and then include this variability directly into the estimation process.

CONCLUSION

Recommended is the use of the Gold Standard estimator when there is a sample of 365 daily dose observations, whether these daily doses (exposures) have been estimated, for example by simulation, or directly observed, in other words samples collected directly. Otherwise the Adjusted Gold Standard is suggested as it directly reflects the use of periodic dose (exposure) observations. Caution regarding the sample size, as with any statistical analysis, of the dose (exposure) observations should be exercised when using the Adjusted Gold Standard as its accuracy diminishes with decreasing dose (exposure) sample size.

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