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A comparison of two models for estimating usual intake addressing zero consumptions and non-normality

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Abstract

Various models exist for estimating the usual intake distribution from dietary intake data. In this paper we compare two of these models, the Iowa State University Foods (ISUF) model and the betabinomial-normal (BBN) model and apply them to three different datasets. Intake data are obtained by aggregating over multiple food products and are often non-normal. The ISUF and BBN model both address non-normality. While the two models have similar structures, they show some differences. The ISUF model includes an additional spline transformation for improving the normality of the intake amount distribution, while the BBN model includes the possibility to address covariates such as age or sex. Our analyses showed that for two of the example datasets both models produced similar estimates of the higher percentiles of the usual intake distribution. However, for the third dataset, where the intake amount distributions appeared to be multimodal, both models produced different percentile estimates.

Keywords: betabinomial and normal distribution; BBN; ISUF; transformation; dietary risk assessment; usual intake distribution.

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Introduction

The presence of substances in food, for example pesticide residues, contaminants or vitamins, can have positive or negative health impacts. The evaluation of dietary intake is an essential step in the risk or benefit/risk assessment of these substances. Health effects may be acute reactions to a short-term exposure (e.g. neurological effects of organophosphate pesticides), or may be of a chronic nature as a result of long-term exposure to relatively low concentrations (e.g. immune suppression due to mycotoxins). This paper addresses the assessment of long-term exposure, and specifically the question which of the available models can be used in specific cases.

When considering long-term exposure to substances in food it is not generally possible to specify the precise time period of interest. Therefore, this period is often left unspecified, and it is customary to consider usual intake, which is defined as the long-run average of daily intakes of a substance by an individual. Although usual intake is commonly expressed on a per-day basis it should not be confused with the daily intake data as calculated from the consumption and concentration information for each individual person-day. The estimation of the usual intake distribution is in one way less complex than that of acute intake distribution, because fluctuations in concentrations can often be assumed to average out in the long run. Hence, one can ignore concentration variability, and only the mean concentration of the substance in the various foods is needed. A difficulty of usual intake estimation is that it is not practical to collect food consumption data of individuals over long periods of time. Typically, the available food surveys employ two to seven independent 24-hour dietary recalls (or records) per individual. As a consequence, the direct estimator (mean consumption over the available days per individual) suffers from large sampling error and the corresponding distribution of means over individuals is too wide in comparison to the distribution of true usual intakes.

Statistical models that separate the variation within persons from the variation between persons have proven very useful for the estimation of usual intake (Hoffmann et al. 2002, Dodd et al. 2006). The simpler models (Slob 1993, Nusser et al. 1996, Waijers et al. 2006) require that all individual-days in the dataset have a positive intake. In more advanced models (Nusser et al. 1997, Slob 2006, Tooze et al. 2006, Van der Voet et al. 2007) allowance is made for a non-negligible fraction of individual-days without intake (incidental or episodic intakes). This paper focuses on the latter category.

Consumed foods belong to one of two categories: A. foods with a positive mean concentration, and B. foods where the substance of interest has never been found. People who only eat from category B on a specific day will obviously have a zero intake of the substance. The true intake on a specific day may still be zero even if foods from category A are

consumed, since the concentration in a single food item may be zero even though the mean is positive. However, for the purpose of long-term intake modelling such days will be treated as positive-intake days.

Usual intake may be different for subgroups in the population and/or it may be correlated with person-specific variables such as age, sex and/or income. These phenomena can be efficiently taken into account by statistical models that estimate usual intake as a function of covariates (we use covariate as a general term for both categorical cofactors and continuous covariables).

In this paper, two models for usual intake that allow zero-intake days are compared. Both models are implemented in the Monte Carlo Risk Assessment (MCRA) program (De Boer and Van der Voet 2007), but also in other software, and have already gained some popularity of use (Hoffmann et al. 2002, Boon et al. 2009 in press). We illustrate their use and argue the appropriateness of each model in relation to data and model assumptions.

Material and methods

Models

The two models considered are based on the same principle of separately modelling intake frequencies and intake amounts, followed by an integration step. In this paper a positive intake refers to a day on which an individual consumes at least one food that has a positive average concentration of the substance considered. Modelling intake frequency is the modelling of frequencies of positive intake per individual, whereas modelling intake amount refers to the positive intake amounts themselves. One of the two models considered is called Statistical Exposure Model for Incidental Intakes (STEM.II) by Slob (2006), and betabinomial-normal (BBN) model by De Boer and Van der Voet (2005), but they are essentially the same models, differing only in some details (see Table 1). The BBN model estimates the usual intake and allows for separate modeling of the effect of covariates for both the intake frequency and the intake amount model. The second model is developed at Iowa State University (Dodd 1996, Nusser et al. 1997). Dodd et al. (2006) refer to this model as the Iowa State University Foods (ISUF) model, and we will follow that notation. The ISUF model estimates usual intake but without the option of taking covariates into account. For the calculations in this paper we have used the MCRA program, release 6 (De Boer and Van der Voet 2007).

In chronic risk assessment, the main interest is the fraction of individuals having a usual (daily) intake higher than a health based limit value such as the acceptable daily intake (ADI) or tolerable daily intake (TDI). Usually, food consumption data are available for individuals on two or more days. Although this is not an essential restriction, we only consider the case

that for each individual an equal number of days is reported. Through the assumed independence of consumption data and compound concentration values (a most reasonable assumption) intake amounts of a substance by individual i on day j are calculated by multiplying the consumed amount per kg body weight by the mean concentration, and then summing over all food items. For calculation of the mean concentration, all available concentration measurements on a food are taken. Non-detect measurements were substituted by a suitable fraction of the limit of reporting (LOR). The calculated intake amounts are the basic data used in further modelling of the intake frequencies and intake amounts.

To assess the uncertainty of the outcomes, both the consumption data and the compound concentration values are resampled using the bootstrap method (Efron 1979, Efron and Tibshirani 1993). For each statistic under consideration, an uncertainty distribution is generated and the sampling error of the original dataset is quantified by a 95% uncertainty interval.

Betabinomial and normal (BBN) model

General description

The name of the BBN model refers to a betabinomial (BB) distribution used for modelling intake frequencies, and a normal (N) distribution used for modelling positive intake amounts. Intake refers to a specific substance of interest. Intake frequency modelling concerns the number of days for which an intake is recorded, due to the consumption of foods that may contain the substance. This number of days is assumed to have a binomial distribution, with a binomial index equal to the total observed number of days, and with probability of intake p , which may itself vary between individual persons. In our model, individual probabilities p are assumed to follow a beta distribution. The beta distribution is commonly used for modelling probabilities and has domain (0, 1). The variability between individual intake probabilities is quantified by the so-called overdispersion parameter ϕ (where $\phi = 0$ would indicate that all individuals have the same p , see Detailed description of BBN implementation in MCRA).

Intake amount modelling concerns the amount ingested of the substance on the days that intake of contaminated food takes place. The intake amount for an individual on a specific day (i.e. observed consumption multiplied by average concentration) is assumed to have an approximate normal distribution after a natural logarithmic or power (Box-Cox) transformation. Variation between and within persons is estimated by analysing the transformed positive intake amounts with a linear random effects model. The models for the intake frequencies and the transformed intake amounts can be extended with covariates, for example sex and/or age (such models are called mixed models because they include both random and fixed effects). After fitting the separate models for intake frequency and intake amount, the usual intake distribution is estimated by combining both models. In BBN this is

achieved by sampling a large number of times from both the betabinomial (intake frequency) and normal (usual intake amount) distribution (Monte Carlo integration). The BBN model assumes that the probability of consumption is unrelated to the individual's usual intake amount. See next section for details of the implementation.

In this paper we used the implementation of the BBN model in the MCRA program. While MCRA and the implementation described in Slob (2006) will give very similar results in many cases, some differences exist in the details. The main differences are summarized in Table 1.

Detailed description of BBN implementation in MCRA

Modelling the intake frequency distribution

Let n and n_{pos} be the total number of survey days per individual and the number of days with a positive intake, respectively. Then n_{pos} is modelled using a binomial distribution with binomial totals n and conditional on probabilities p . The probabilities p in turn are assumed to follow a beta distribution. The resulting distribution for n_{pos} is known as the betabinomial distribution. The mean and variance of a beta distribution are:

$$\alpha / (\alpha + \beta)$$

and

$$\alpha \beta (\alpha + \beta + n) / [(\alpha + \beta)^2 (\alpha + \beta + 1)], \text{ respectively.}$$

Re-parameterizing by $\pi = \alpha / (\alpha + \beta)$ and $\phi = 1 / (\alpha + \beta + 1)$ is a more stable and interpretable parameterization. It can be shown that the mean and variance of n_{pos} are equal to:

$$n \pi$$

and

$$n \pi (1 - \pi) [1 + (n - 1) \phi], \text{ respectively.}$$

Note that the first part of the variance $n \pi (1 - \pi)$ equals the binomial variance; the second part adds the effect of the so-called overdispersion, quantified by the overdispersion factor ϕ .

Fitting the beta-binomial model with maximum likelihood gives estimates $\hat{\pi}$ and $\hat{\phi}$ for the parameters π and ϕ . As regards notation, estimates are denoted by a hat (^). Back-transformation gives the following estimates for the standard Beta distribution parameters α and β :

$$\hat{\alpha} = \hat{\pi}(1 - \hat{\phi}) / \hat{\phi}$$

$$\hat{\beta} = (1 - \hat{\pi})(1 - \hat{\phi}) / \hat{\phi}$$

The distribution of the probability that an individual has a positive intake on any single day is then modelled by Beta($\hat{\alpha}$, $\hat{\beta}$).

Modelling the positive intake amounts

First, to achieve a better normality, the positive intake amounts are transformed. The user can choose a logarithmic transformation $transf(ypos) = \ln(ypos)$ (no parameters to be estimated) or a power transformation $transf(ypos) = ypos^{pow}$ (where the parameter pow is to be estimated). In the latter case the optimal power is determined on the grid $\{10, 2, 1, \frac{1}{1.5}, \frac{1}{2}, \frac{1}{2.5}, \frac{1}{3}, \frac{1}{3.5}, \dots, \frac{1}{100}\}$, with a further refinement grid search around the best fitting value. If a power $\frac{1}{100}$ gives the best fit in this grid search, then the logarithmic transformation is selected (Note that a logarithmic transform corresponds theoretically to $pow=0$). The goodness-of-fit is determined by minimising the residual sum of squares: $\sum (z_{(i)} - \beta \cdot ypos_{(i)}^{pow})^2$ of a regression of normal Blom scores on the power-transformed intake amounts. Normal Blom scores are (Blom 1958):

$$z_{(i)} = \Phi^{-1}\left(\frac{i - \frac{3}{8}}{n + \frac{1}{4}}\right)$$

where i is the rank of the n^{th} non-zero intake amount, n , the total number of non-zero intakes and $\Phi^{-1}(\cdot)$ is the inverse of the standard normal cumulative distribution function.

The transformed positive intake amounts are modelled in a maximum likelihood analysis with random terms *person* and interaction *person.day* to estimate the between- and within-person variance component:

$$transf(ypos_{ij}) = \mu + \underline{c}_i + \underline{u}_{ij}$$

where $transf(ypos)$ is a transformed intake amount, and where $\underline{c}_i$ and $\underline{u}_{ij}$ are the between-person effect and within-person effect, respectively. These effects are assumed to be normally distributed with $N(0, \sigma_B^2)$ and $N(0, \sigma_W^2)$, respectively. The maximum likelihood procedure gives estimates m , s_B^2 and s_W^2 .

Calculating the usual daily intake distribution

The usual intake is defined as the expected intake amount per day (over both consumption and non-consumption days) of a random individual. The distribution is estimated by Monte Carlo integration, where a simulated intake from the distribution of positive intakes is multiplied by a simulated value from the distribution of individual intake probabilities.

First, a large number of positive intakes on the transformed scale are simulated as $m + z_i$, where z_i is a random value from the $N(0, s_B^2)$ distribution. Secondly, these values are backtransformed to the natural scale and a bias-correction is applied so that the values represent unbiased estimates of the expected value of positive intakes at the natural scale. For a logarithmic transformation there is an exact relation and the bias-corrected backtransformation is

$$ypos_i = \exp\left(m + z_i + \frac{1}{2}s_w^2\right)$$

For a power transformation with power pow a Taylor approximation for bias correction is used (Dodd et al. 2006) and the approximately bias-corrected backtransformation is:

$$ypos_i = (m + z_i)^\lambda \cdot \left(1 + \frac{1}{2}\lambda(\lambda - 1)s_w^2\right)$$

where $\lambda = 1/pow$ is the inverse of the estimated power.

The distribution of $ypos_i$ obtained thus far represents values expected for positive intakes. An individual will not have a positive intake on all days but only on a fraction of days. For each value of $ypos_i$ a probability p_i is drawn from the estimated $\text{Beta}(\hat{\alpha}, \hat{\beta})$ distribution to represent this fraction, and these values are multiplied to obtain an estimate of the usual intake for this individual:

$$y_i = p_i \cdot ypos_i$$

Extended with a covariable and/or cofactor the regression model for intake frequencies can be written as:

cofactor:	$\text{logit}(\underline{x}) = \beta_{0k}, k=1 \dots K$
covariable:	$\text{logit}(\underline{x}) = \beta_0 + \beta_1 f(x_1; df),$
cofactor + covariable:	$\text{logit}(\underline{x}) = \beta_{0k} + \beta_1 f(x_1; df), k=1 \dots K$
cofactor + covariable + interaction:	$\text{logit}(\underline{x}) = \beta_{0k} + \beta_{1k} f(x_1; df), k=1 \dots K$

where π is the expected intake frequency, K is the number of levels of the cofactor, x_l is the covariable, f is a spline or polynomial function and df the degrees of freedom of the spline or the degree of the polynomial. In the program the optimal degrees of freedom can be calculated by a backward or forward search.

Also the positive intake amounts can be modelled to be dependent on a cofactor and/or covariable. The model for the transformed intake amount is then:

cofactor:	$transf(y_{ij}) = \beta_{0k} + \underline{c}_i + \underline{u}_{ij}, k=1 \dots K$
covariable:	$transf(y_{ij}) = \beta_0 + \beta_1 f(x_l; df) + \underline{c}_i + \underline{u}_{ij}$
cofactor + covariable:	$transf(y_{ij}) = \beta_{0k} + \beta_1 f(x_l; df) + \underline{c}_i + \underline{u}_{ij}, k=1 \dots K$
cofactor + covariable + interaction:	$transf(y_{ij}) = \beta_{0k} + \beta_{1k} f(x_l; df) + \underline{c}_i + \underline{u}_{ij}, k=1 \dots K$

where $transf()$ represents the chosen transformation function, with the same notation as used before.

Iowa State University Foods (ISUF) model

General description

The ISUF model is based on a model for estimating the usual intake distribution from data sets with positive intakes only, as described by Nusser et al. (1996). Similarly to the BBN model, frequencies and amounts are independently modelled and variation between and within persons is estimated by analysing the transformed positive intake amounts with a linear random effects model. The difference is that, in addition to a logarithmic or power transformation, ISUF applies a spline transformation using grafted polynomials to meet the normality assumption (see Detailed description of ISUF implementation in MCRA for details). By increasing the number of parameters of the grafted polynomial, the procedure ensures that the adjusted positive intake values have a normal distribution. The modelling of the positive intake amounts via grafted polynomials also allows for heterogeneity of variance (in contrast to BBN), e.g. the concept that some individuals are more variable than others with respect to their consumption habits. Nusser et al. (1997) and Dodd (1996) describe the estimation of usual intake from data sets with a substantial amount of zero intake days. They separately model zero intake on part or all of the days via the estimation of intake frequencies.

The ISUF model is available in the C-SIDE program (Dodd 1996) and the main features have been implemented with some differences in MCRA (De Boer and Van der Voet 2005, 2007). The implementation of the ISUF model in MCRA is described in more detail in the next section. In Table 2, the main differences in implementation of the ISUF model in MCRA and C-SIDE are described.

Detailed description of ISUF implementation in MCRA

Modelling the intake frequency distribution

The individual intake frequency distribution is approximated via a number of classes (default 21, other values can be selected by the user) arranged by the proportion of days on which there is a positive intake (p_m). Using a binomial distribution for each class, the fraction of individuals in each class (θ_m ; $m = 0, \dots, M$) is estimated by optimising the fit of the predicted proportions of individuals with 0, 1, 2, ... intake days to the observed proportions. The number of parameters to be estimated is usually higher than the number of possible outcomes for an individual (e.g. 3 when there are two days per individual), and therefore a smooth approximation is made using a modified minimum chi-squared estimator. See Dodd (1996) for details. Only the fraction of non-consumers (θ_0) is estimated separately with no restriction to be similar to the other θ_m . It can be noted that the distribution of individual intake probabilities can be better estimated when the number of days per individual in the consumption survey becomes higher. With only 2 days per individual the procedure gives a rather artificial distribution, often with an estimated θ_0 of zero. This step can be time-consuming. Therefore, the number of iterations in the estimation procedure can be limited by the user. In our experience it is not necessary to use 50,000 iterations as in Dodd (1996) and we use 5000 (other value can be chosen by the user).

Modelling the positive intake amounts

Step 1: power or log transformation

See description of the BBN model.

Step 2: spline fit

To achieve a better normality, a second transformation (optional) is performed: a spline function $t = g(z)$ is fitted to the logarithmically or power transformed data t as a function of the normal Blom scores. The spline function is a grafted polynomial consisting of cubic polynomials between $p = 3$ joint points (knots) and linear functions in the two outer regions. The intake amounts are transformed by interpolating from t to $x = g^{-1}(t)$, using the fitted spline function.

After a successful transformation the intake amounts x will resemble Blom normal scores and their mean and total variance will therefore be approximately 0 and 1. The normality of the transformed values x is checked with the Anderson-Darling test. In the case of a spline

transformation, if normality is rejected at the 85% confidence level, then the number of knots p is increased and the spline fit is repeated (until a maximum of 22 knots).

Step 3: estimation of the parameters of the usual intake distribution

Variance components for between and within-person information are fitted to the transformed non-zero intake amounts x using the model:

$$x_{ij} = x_i + u_{ij}$$

$$x_i \sim N(\mu, \sigma_B^2); \quad u_{ij} \sim N(0, s_i^2); \quad E(s_i^2) = \sigma_0^2; \quad \text{var}(s_i^2) = \sigma_w^2$$

In this model the total variance of the intake amounts is divided into a between-person component and a within-person component. The within-person variance component can be heterogeneous, that is, it can be different for different individuals. In the model the between-person variance σ_B^2 and the mean and the variance of the within-person variance component distribution (σ_0^2 and σ_w^2) are estimated using standard statistical methods (ANOVA). Further, a test statistic $MA4$ is calculated to test whether the heterogeneity of variances is significant (see Dodd 1996 for details).

The estimate s_B^2 of the between-person variance is the basis for the estimation of the distribution of usual intake. The distribution of usual intakes on non-zero intake days in the x scale is represented by a set of 400 normal Blom scores (which themselves represent the standard normal distribution) multiplied by s_B : $x_i = s_B z_{(i)}$. The same calculation is applied to user-requested percentiles $z_p = \Phi^{-1}(p)$.

Step 4: back transformation and estimation of usual intake

The 400+ values x_i are back-transformed to the original scale. This is simple if no spline function has been estimated. If a spline function has been used, then it is a rather complicated procedure, because the spline function g was developed for intake amounts, not usual intakes. The following steps are made:

1. First the 400+ values x_i are expanded in a set of 9 x 400 values representing the distribution of intake amounts around each of the 400 points; These 9 x 400+ values are back transformed using the functions g and f , and the sets of 9 values are then recombined by weighted averaging into 400 usual intake values y_i . The precise amount of expansion and weighting takes into account the within-person variance component and the estimated heterogeneity of variances (Dodd 1996).

2. A spline function g_1 , especially adapted for usual intakes, is now fitted to the 400 data pairs (x_i, t_i) , where $t_i = f(y_i)$;
3. Finally the usual intakes on non-zero intake days are represented by the back-transform using this improved function: $y_i = f^{-1}(g_1(x_i))$.

The user-requested percentiles y_p are the additional values ($i > 400$) in the 400+ set. The 400 y_i values define the cumulative distribution function by:

$$F(y_i) = \frac{i - \frac{3}{8}}{400 + \frac{1}{4}}.$$

The distribution is adapted in order to account for days with zero intake of individuals (defined here as individuals who have a positive probability of intake on any day, and therefore a non-zero usual intake).

Modelling usual daily intake

The estimated distribution of individual intake probabilities $(\hat{\theta}_0, \dots, \hat{\theta}_M)$ is used to transform the distribution of usual intake on non-zero intake days (F_y) to the distribution of usual intake for consumers (F_C) and finally to the distribution of usual intake for the entire population (F_U). These transformations are based on the relation:

$$F_U(u) = \theta_0 + \sum_{m=1}^M \theta_m F_y(u/p_m)$$

which basically says that to obtain a certain level of usual intake u we should consider a different level (u/p_m) for the class of consumers which consume only on a fraction p_m of days. See Dodd (1996) for details of the computational procedure. Linear interpolation based on the 400 values of the F_y distribution is then used to compute representations of the cumulative distribution functions for consumers only and the entire population.

Model adequacy

Both the BBN and ISUF model distinguish variation between individuals from variation between days of the same individual, and they assume normality of the between-individual term in order to derive usual intake percentiles. Departures from normality may give biased estimation of the model parameters and, hence, may give wrong inference about the usual intake distribution. So a check of model adequacy is necessary.

There are three types of residuals that may be considered for checking model adequacy: 1) the set of best linear unbiased predictors (BLUPs, also called random effects, see e.g. Robinson 1991), representing the individual deviations from the average, 2) the set of residuals on the level of days (conditional residuals), and 3) the sum of 1 and 2, which is the set of deviations per individual and day from the overall average (marginal residuals). See Testing for normality in mixed models for a more detailed description of the three types of residuals. Gurka et al. (2006) showed that near-normality of the marginal residuals implies near-normality of both the random effects and the conditional residuals. MCRA provides diagnostic checks based on marginal residuals.

Formal normality tests are available to provide information about the adequacy of the model and/or the validity of its associated assumptions. The Anderson-Darling (AD) goodness-of-fit statistic (Stephens 1974) is especially sensitive towards deviations in the tail regions, and has been used more for tail risk applications (Nusser et al. 1996). An alternative is to consider graphical displays of residuals like the normal quantile–quantile (q-q) plot. In the BBN model the intake amounts are transformed before analysis either logarithmically or by a power transformation. The choice of power is guided by the AD test statistic to approach normality of the positive intake amounts as well as possible. Nevertheless, the transformed data may still show considerable non-normality, and (visually) checking normality should be a standard diagnostic procedure.

The ISUF model has a more flexible data transformation than BBN, which increases in complexity in order to actually guarantee normality of the transformed values (on the guidance of AD tests). It is therefore questionable whether there is much purpose in checking normality after the full ISUF data transformation.

For intake amount distributions that show multimodal patterns, transformation to normality using the log or power transformation can be expected to fail. The multimodal pattern is a consequence of aggregation over multiple foods in circumstances where foods are not consumed on all days and/or foods have highly different average contamination levels. The resulting intake amount distribution forms a mixture with various peaks related to the diverse foods. Multimodality may also be caused by different subpopulations with distinct consumption patterns.

Testing for normality in mixed models

The linear mixed model is:

$$y_{ij} = \mu + \alpha_{c(i)} + \beta_i + \varepsilon_{ij} ,$$

for log or power transformed positive intake amount data y_{ij} of individual i ($i=1, \dots, n$) on day j ($j=1, \dots, n_i$), where $\alpha_{c(i)}$ represents the fixed effects for category c to which individual i belongs (e.g. age, sex), and where β_i and ε_{ij} are uncorrelated normally distributed random terms for between-person and within-person variation, with variance σ_B^2 and σ_W^2 , respectively.

For the linear mixed model, three types of residuals are defined.

Marginal residuals are: $\xi_{ij} = y_{ij} - \mu - \alpha_{c(i)} = \beta_i + \varepsilon_{ij}$,

conditional residuals are: $\varepsilon_{ij} = y_{ij} - \mu - \alpha_{c(i)} - \beta_i$,

and BLUPs or random effects: β_i .

Gurka et al. (2006) show that, if the marginal error term after transformation results in near normality, then the random effects and conditional error term will have approximate Gaussian distributions. If normality is considered an acceptable assumption, then the usual intake distribution for category c is also a normal distribution with mean $\mu + \alpha_c$ and variance σ_B^2 , which can be easily sampled (as done in the BBN method).

Case studies

We compare the methods by applying them to real data sets. Full validation of the results is not possible with real data because true usual intake distributions are unknown. Therefore the results of both models can only be compared to each other.

- Case 1 (acrylamide) represents intake data with few zeros. Covariates are not considered.
- Case 2 (glycoalkaloids) relates to intake amounts that are a function of a set of covariates, here age and sex.
- Case 3 (patulin) represents data with a bimodal intake distribution.

In all three studies, the uncertainty due to limited concentration and consumption data was quantified by a bootstrap uncertainty analysis using 500 re-sampled sets of the consumption and concentration data. Empirical 95% uncertainty intervals were used to describe the uncertainty in selected percentiles of the usual intake distribution.

The purpose of this study is to compare models, not a detailed analysis of cases. Non-detects were in all studies assumed to be zero concentrations, although in a real risk assesment this could lead to an underestimation of the usual exposure.

Case 1: Acrylamide, approximate normality after power transformation

Acrylamide has been detected in foods since 2002 and is potentially genotoxic and carcinogenic in humans. It can be formed by heating of starchy foods, like French fries, biscuits and crisps. Consumption data of 1279 Dutch children aged two through six years, recorded on two non-consecutive days, were used (Ocké et al. 2008). These food consumption data were combined with acrylamide levels as reported in Boon et al. (2009 in press) and obtained from the Dutch Food and Consumer Product Safety Authority (VWA). We modelled the usual intake distribution of acrylamide using both the BBN and ISUF model, transforming intake amounts of acrylamide with a power transformation.

In the food consumption survey, 176 foods possibly containing acrylamide (these were the foods for which positive acrylamide concentrations have been measured) were recorded. They were linked to 25 food groups. A total of 189 samples from each food group (e.g. cookies, crisps, chips and Dutch spice cake) were available with measured acrylamide concentrations, 13 of which were non-detects (samples with a level below the limit of reporting). For more details on the linkage between single foods and food groups, see Boon et al. (2009 in press) On 95% of the consumption days, at least one of the 176 foods was consumed. In more detail, 1172 (92%) out of 1279 children consumed at least one of the foods on both study days, 94 (7%) children on only one study day, and 13 (1%) children on none of the study days.

Food consumption per day was multiplied with the mean acrylamide level of that food, and summed over all foods to obtain a distribution of intake amounts (ng/kg bw/day). Data transformation (power 0.262) was necessary to obtain a reasonable normal distribution for the positive intake amounts (Figure 1a, 1b). Based on the q-q plot (Figure 2a) the transformed data could be considered as reasonably normal, although normality was rejected in a formal test ($AD = 1.76$, $p < 0.005$). Normality was improved after the additional spline transformation of ISUF, see Figure 2b: $AD = 0.57$, $p > 0.15$).

Based on visual inspection of the q-q plots, we expect the relatively simple BBN model to give an adequate exposure assessment. It may be noted that a small deviation is seen in the lower part of the distribution, but in risk assessment the interest is in the upper part. The normality assumption of the underlying distributions seems reasonable and the more complex ISUF model may not be needed.

In Figure 3, the distributions for the intake frequencies (a) and positive intake amounts (b) as estimated with BBN are shown. The average frequency for acrylamide intake on any

day was estimated as 0.953, with an overdispersion factor 0.178. These values imply a distribution of intake frequencies among individuals as shown in Figure 3a. Thus, most people consume foods containing acrylamide on a daily basis, but there are also some individuals who do so less frequently. The average transformed intake amount was estimated at 5.06 (s.e. 0.03), and the between and within individual variances at this scale were estimated at 0.27 and 1.95, indicating much more variation in acrylamide intake within individuals than between individuals.

Table 3 shows estimated percentiles of the usual intake of acrylamide for BBN after a power transformation, and ISUF after a power transformation with and without an additional spline transformation. As was expected, the three models give similar results, with for example p99 of usual intakes between 1317 and 1344 ng/kg bw/day. The percentiles relate to the usual intake distribution, and are much lower than those in Figure 1 due to the large variation within individuals

Case 2: Glycoalkaloids, covariate dependency of intake

In this example concerning glycoalkaloids, we demonstrate the ability to model usual intake of substances as a function of covariates, such as age and sex. We used the day food consumption patterns of 6187 persons aged 1 through 80 years and recorded on two consecutive days (DNFCS-3, Kistemaker et al. 1998), and combined it with glycoalkaloid concentrations in potatoes as obtained from Ruprich et al. (2009).

Glycoalkaloids occur mainly in potato. Not only potatoes eaten as such were included but also potato as an ingredient of more complex dishes. This was done by the use of the Dutch food conversion model which converts foods as coded in the different Dutch food consumption surveys in their raw agricultural commodities, including weight fractions (Van Dooren et al. 1995).

The glycoalkaloid intake from 62 foods was considered. In total, 372 positive glycoalkaloid concentrations and 67 non-detects were available, here quantified by the sum of solanin and chaconin concentrations. Concentrations were corrected for processing effects of cooking or frying (Ruprich et al. 2009). Potato was consumed on 80% of the consumption days. Among the 6187 individuals, 4061 (66%) consumed potato on both study days, 1785 (29%) on only one of the days while 341 (6%) individuals did not record the consumption of potato during both study days.

The primary model used for these data was BBN, including an analysis of the effect of covariates age and sex on the usual intake. The intake frequency of glycoalkaloids was not found to depend on sex, while age dependency could be modelled with a spline function with 4 df. Intake frequencies were highly variable between persons, ranging from less than 50% to over 95% (see Figure 4a). A power of 0.339 was found to be optimal for approximating

normality of the positive intake amounts. Intake amounts were dependent on both age and sex (see Figure 4b). For males, a slightly higher intake per kg body weight was found than for females. The age effect could be modelled with a spline with 4 df. The difference between males and females was not significant over the age range (no interaction term was necessary in the model). The between and within individual variances on the power-transformed scale were estimated at 0.30 and 1.92, indicating much more variation in glycoalkaloid intake within persons than between persons. A histogram of the marginal residual distribution after correcting for the covariates age and sex is shown in Figure 5a. In spite of the power transformation there was still a strong and significant deviation from normality ($AD = 38.19$, $p < 0.005$), which casts doubt on the applicability of the BBN model to model the usual intake of glycoalkaloids. Some example results for the p99 of usual intake are shown in Table 4.

In order to make a comparison with ISUF, we ran both BBN and ISUF without those covariates (since ISUF has no facility for covariates). The AD test applied to the intake amounts after a power transformation followed by a spline transformation detected only negligible deviation from normality, $AD = 0.54$, $p > 0.2$ (see Figure 6). Results for p99 are shown in Table 4. When no covariates are included, the results from both models are similar, and the additional spline transformation does not make a difference.

A run with ISUF applied on subsets of the data, in particular, males and females, aged 1 through 5 and 30 through 40, confirmed the age effect earlier found with BBN. However, for sex, opposite age-effects are estimated. Whereas BBN estimates higher percentiles for males, ISUF estimates higher percentiles for females. A closer look at the results for each subpopulation shows that the variation between males is smaller than between females. As a result, the usual intake distribution for males is narrow compared to the distribution for females. Further, the uncertainty intervals are wider for ISUF than for BBN (see Table 4)

Case 3: Patulin, bimodal distributions of intake

This example demonstrates a case where normality cannot be achieved using a simple log or power transformation. A relevant question is whether the more complex spline transformation of the ISUF model would be appropriate.

Patulin is a mycotoxin which is mainly found on apple products. Consumption data of 1279 Dutch children aged two through six years, recorded on two non-consecutive days, were used (Ocké et al. 2008). The concentration data for patulin was derived from monitoring programmes performed in the Netherlands in 2002-2006 by VWA. Levels are reported in Boon et al. (2009, in press). Patulin was detected in two foods (apple juice and apple sauce canned) which were linked to 83 foods as recorded in the food consumption survey of young children. In total, 45 samples were available, 13 concentration measurements were detected, the number of non-detects was 32. The 83 apple products in the food consumption survey were

consumed on 90% of the days. In more detail, among the 1279 children in this study, 1076 (84%) consumed at least one of these apple products on both study days, 160 (12%) on only one study day, and 43 (3%) on none of the study days.

The power transformation was close to zero and was replaced by a logarithmic transformation. The logarithmic transformation was not sufficient to approach normality (see Figure 7b, where the distribution of the log transformed intake amounts is shown). In this mixture distribution, two or three constituent intake distributions are visible. To convert the multimodal intake amount distribution into an approximately unimodal distribution, a spline function with 11 knots was needed (Figure 7c). After fitting the spline to the logarithmic transformed intake data (Figure 7d), normality was not rejected according to the AD statistic ($AD = 0.49, p > 0.25$).

Fitting the BBN model and comparing the results with likelihood ratio tests revealed a dependency of intake amount on age (see Figure 8a, b). However, modelling age did not explain the bimodal nature of the distribution. In Figure 9, a histogram (a) of the marginal residual distribution is shown together with the corresponding q-q plot (b). It is apparent that normality assumptions were violated ($AD = 4.07, p < 0.005$).

This example demonstrates how nonnormality can arise as a result of aggregating foods. Figure 10 shows a number of intake amount distributions of patulin after a logarithmic transformation. Figure 10(a-l), show the distributions for foods as recorded in the food consumption survey for cases where 100 or more positive intake data are available.

In Table 5, it is shown for a selected percentile (p99) that the ISUF and BBN results were different in this case. The BBN usual intake values, both age specific and without any covariate, were all higher than the overall ISUF estimate.

Discussion

Two models for estimating the long-term exposure distribution of dietary intake of substances on foods have been compared. The betabinomial-normal model (BBN) estimates the usual intake distribution whether or not as a function of covariates. The Iowa State University Foods model (ISUF) estimates the usual intake distribution, but cannot address covariates in the statistical model (although in the C-SIDE implementation of ISUF a priori data adjustments can be made for non-person-specific biases such as season or day of the week). To meet the normality assumptions, data are transformed first by a log or power function, and, in case of ISUF, this can be followed by an additional spline transformation to achieve normality. Both methods separately estimate the individual intake amount distribution and the distribution of individual intake frequencies before calculating the unconditional usual intake distribution.

For dietary exposure data, even after a log or power transformation, non-normality occurs frequently in our experience, and it is worthwhile to have a closer look at this phenomenon. Intake amounts are calculated by multiplying food consumption data with average concentration levels of substances present in various foods. Each intake amount may be the sum of contributions due to the consumption of various foods and, generally, the resulting distribution is a mixture of distributions related to individual foods. When these foods differ in consumption rates and/or concentrations, multimodal distributions will arise. But even if the intake of a substance appears to originate from only one food the intake distribution may be a mixture: the food may be consumed as an ingredient of a more complex dish or may be processed in a number of ways with each processing type having different processing factors. Even when single food distributions are unimodal, the aggregate distribution may be multimodal, and this effect is most pronounced when not all foods are consumed on all days.

One can easily imagine some people eating cooked potatoes on a fraction of the days, others fried, some as an ingredient like potato flour or people that do not consume potatoes at all. Also, people vary their choice of potato product between days. It is obvious that transforming data in order to have normal distributed intake values is a huge simplification of the rather complex intake patterns lying behind it. The patulin case illustrates this. Figure 10 shows that, after a logarithmic transformation, constituent distributions are all unimodal, but the total intake distribution of patulin is definitively multimodal (Figure 7b).

Given that non-normality is common for aggregated intake, what is the role of formal normality tests and more informal graphical procedures? With only slight deviations from normality and with large sample sizes (as we often have) formal normality tests easily give significant results. Testing normality, e.g. using the Anderson-Darling (AD) test, is in many dietary risk applications like asking a question one already knows the answer to. Therefore, our proposal is to have a closer look at the non-normal behaviour of the data. We advocate the use of graphical methods like the q-q plot and histograms of the estimated marginal error distribution to study the applicability of the normal model and not to rely on test results.

The acrylamide case illustrates our proposal. According to the AD statistic, a power transformation is insufficient to approximate normality, but an additional spline transformation shows no lack of fit. However, the q-q plots for BBN and ISUF are visually very similar (Figure 2). Non-normal behaviour is mainly found in the left tail of the distribution, whereas for substances with negative health effects as acrylamide the individuals at risk are at the right-tail of the distribution. The resulting percentiles are all in the same range and confirm our idea that it is acceptable to use BBN to estimate the usual intake distribution.

The patulin case demonstrates an intake amount distribution where non-normality manifests itself as a multimodal distribution. The results in Table 5 show that the estimates of the p99 percentiles for BBN (without any covariates) and ISUF are highly different and lie far outside each other's uncertainty intervals. The BBN estimate is much higher because a unimodal normal distribution is fitted where a multimodal would have been appropriate leading to an overestimation of the upper tail. We conclude that BBN here is likely to be unreliable, and it should not be used. In ISUF, intrinsic to the method, normality is always achieved.

The glycoalkaloid case is an intermediate one. Based on the q-q plot, the applicability of BBN remains questionable. However, the estimates of the p99 percentiles for BBN (without covariates) and ISUF match remarkably well (see Table 4) and it is not clear that BBN is inappropriate for intake assessment.

We conclude that the choice of the appropriate model for modelling usual intake based on incidental consumption patterns should be made on a case-by-case basis. When a logarithmic or power transformation results in approximately normal data, the BBN model is preferred over the more complex ISUF model. Moreover, ISUF is not applicable when the intake distributions depend on covariates, whereas BBN is. BBN is fairly robust against departures of normality as shown in the acrylamide and glycoalkaloid cases, where estimated percentiles of BBN are in the same range as results obtained with ISUF. Even when the normality assumption is questionable both methods may provide similar results, as in the glycoalkaloids case. The patulin case presents an example of bimodal or perhaps multimodal distributed intakes. In Figure 7b, three constituent intake distributions appear to be visible, probably relating to different consumed foods (see Figure 10). Since the additional spline transformation made the distribution closer to normal (Figure 7d), the ISUF model seems to be a better choice in this case. However, theoretical considerations and preliminary results using a simulation model indicate that also the ISUF model may not give reliable results for distributions of intakes that result from consumption of various foods. Based on these results we conclude that more research is necessary to develop a method to perform intake calculations based on multimodal intake distributions.

While the spline transformation in ISUF will always give a normal distribution for the transformed intake amounts, this transformation itself may destroy the assumptions necessary for the variance components model used for estimating the variance of usual intake. In our three examples, the ISUF spline transformation needed 6, 11 and 11 knots in the spline, respectively, to achieve normality. Clearly, higher numbers increase the nonlinearity of the transformation and, eventually, may violate mixed model assumptions as uncorrelated errors and additivity on the transformed scale.

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In both models transformations may be chosen based on parameters that have to be estimated from the data. These are the power transformation in BBN and ISUF and the ISUF spline transformation. Gurka et al. (2006) concluded that in the context of linear mixed models variance components may be estimated with bias when an estimated transformation of data is being used. In their case they considered the power transformation but the same reasoning seems valid for a spline transformation.

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If intakes are dependent on covariates (e.g. age, or sex) then the ISUF model as implemented in MCRA 6 can only be applied on subsets of the data, which implies a stronger dilution of the information in the data as compared to the covariate analysis as employed in BBN. This is illustrated by the increased size of the uncertainty intervals of ISUF compared to BBN.

23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 **Acknowledgement**

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Table 1. Differences between the BBN model as implemented in MCRA (see Detailed description of BBN implementation in MCRA) and as discussed in Slob (2006)

Table 2. Differences between implementations of the ISUF model in MCRA (see Detailed description of ISUF implementation in MCRA) and C-SIDE (Dodd 1996).

Table 3. Estimated percentiles of usual intake (ng/kg bw/d) of acrylamide (with 95% uncertainty intervals).

Table 4. Estimated percentile (p99) of usual intake (ng/kg bw/d) of glycoalkaloids according to four models (with 95% uncertainty intervals). For ISUF (age/sex), subpopulations of females and males aged 1 through 5 and 30 through 40 are analysed. The number of consumers (n) is 6187 unless otherwise indicated.

Table 5. Estimated percentile (p99) of usual intake (ng/kg bw/d) of patulin (with 95% uncertainty intervals).

Figure 1. Distribution of intake amounts of acrylamide before (a) and after (b) 0.262th power transformation. The best fitting normal distribution is shown for comparison.

Figure 2. The q-q plot of the acrylamide intake amounts after power transformation (a) as performed in BBN (AD = 1.76, p<0.005) and after power and spline transformation (b) as performed in ISUF (AD = 0.57, p>0.15).

Figure 3. Estimated beta density for acrylamide intake probabilities (a) and backtransformed cumulative normal density function for positive usual intake amounts (b) obtained with BBN.

Figure 4. Means of observed and modelled glycoalkaloid intake frequencies (a) and intake amounts (b). All curves are splines with 4 df. The outer curves in the intake frequency plot show large individual variation by 2.5% and 97.5% percentiles of the fitted betabinomial distribution. The intake amount plot shows separate curves for males (upper) and females (lower). Vertical bars in the intake amount plot are between- (left) and within-individual (right) standard deviations.

Figure 5. Histogram together with best fitting normal distribution (a) and q-q plot (b) for the marginal residuals for the glycoalkaloid intake after fitting the BBN model as a function of age and sex. A significant deviation from normality is observed according to the AD statistic (AD = 38.19, p<0.005).

Figure 6. Histogram together with best fitting normal distribution (a) and q-q plot (b) for the intake amounts of glycoalkaloids after power and spline transformation using the ISUF model. Normality is not rejected according to the AD statistic (AD = 0.54, p>0.2).

Figure 7. Intake amounts of patulin: natural scale (a), after logarithmic transformation (b; ISUF), and after an additional spline transformation (d; ISUF). Graph c shows the spline fit of the logarithmic-transformed intake amounts as function of the theoretical residuals. The best fitting normal distribution is shown for comparison.

Figure 8. Modelling of daily intake frequency (a) and intake amount (b) of patulin as a function of age. The outer curves in the intake frequency plot show large individual variation by 2.5% and 97.5% percentiles of fitted betabinomial distribution. Vertical bars in the intake amount plot are between-person (left) and within-person (right) standard deviations.

Figure 9. Histogram together with best fitting normal distribution (a) and q-q plot (b) for the marginal residuals for patulin after fitting the BBN model with age effect. Deviation from normality is significant according to the AD statistic (AD = 4.07, p<0.005).

Figure 10. Intake amounts of patulin after a logarithmic transformation for foods as recorded in the food consumption survey (a) apple juice unsweetened; (b) apple sauce canned; (c) lemonade squash; (d) fruit drink concentrate; (e) syrup fruit all tastes; (f) lemonade three fruit drink; (g) lemonade fruit drink 15-20 mg vitamin C; (h) fruit drink Wicky; (i) syrup average dilution; (j) yogurt flavoured fruit drink Yoki; (k) ice based on fruit; (l) apple syrup. The best fitting normal distribution is shown for comparison. Despite the fact that all AD statistics are significant, the visual impression is that all distributions are approximate lognormal.

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- The paper is not intended for a special issue.

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Table 1. Differences between the BBN model as implemented in MCRA (see Detailed description of BBN implementation in MCRA) and as discussed in Slob (2006)

	MCRA	Slob (2006)
parameterization of beta distribution	expected frequency π , overdispersion factor φ	classical parameters (α, β)
data transformation	logarithmic or power	logarithmic
covariable (e.g. age) model	polynomial or cubic smoothing spline (Hastie & Tibshirani 1990)	Various models e.g. chosen from a family of non-monotone regression functions (Slob 2002).
cofactor (e.g. sex) model	π as a function of cofactor; interaction with covariable is optional	selected regression parameters and/or variance in covariable model may be estimated separately for levels of cofactor
bootstrap uncertainty limits	yes	no

Table 2. Differences between implementations of the ISUF model in MCRA (see Detailed description of ISUF implementation in MCRA) and C-SIDE (Dodd 1996).

	MCRA	C-SIDE
use of sampling weights	no	yes
adjustment for nuisance and/or period effects	no	yes
number of classes in frequency model	21 (default, can be changed)	51
estimation of intake probability distribution parameters	5,000 iterations (default, can be changed)	50,000 iterations
modelling correlated within-individual amounts	no	yes
percentiles calculated for	grid of 400 points + user-defined values	grid of 400 points
bootstrap uncertainty limits	yes	no

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Table 3. Estimated percentiles of usual intake (ng/kg bw/d) of acrylamide (with 95% uncertainty intervals).

	BBN		ISUF without spline		ISUF with spline	
p50	642	(566, 724)	641	(568, 724)	621	(545, 690)
p95	1093	(902, 1270)	1108	(960, 1267)	1079	(937, 1238)
p99	1342	(1053, 1585)	1344	(1127, 1583)	1317	(1116, 1547)
p99.9	1655	(1350, 2040)	1597	(1290, 1931)	1580	(1270, 1878)

Table 4. Estimated percentile (p99) of usual intake (ng/kg bw/d) of glycoalkaloids according to four models (with 95% uncertainty intervals). For ISUF (age/sex), subpopulations of females and males aged 1 through 5 and 30 through 40 are analysed. The number of consumers (n) is 6187 unless otherwise indicated.

Model				
total population				
BBN				
186 (164, 205)				
ISUF				
183 (168, 202)				
BBN (age/sex)	female, age 3	male, age 3	female, age 35	male, age 35
	260 (230, 289)	281 (242, 306)	128 (108, 139)	136 (116, 151)
ISUF (age/sex)	female, age 1-5 (n = 212)	male, age 1-5 (n = 233)	female, age 30-40 (n = 592)	male, age 30-40 (n = 500)
	301 (210, 518)	212 (193, 596)	134 (101, 159)	118 (97, 299)

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Table 5. Estimated percentile (p99) of usual intake (ng/kg bw/d) of patulin (with 95% uncertainty intervals).

Model		
	age 2	age 6
BBN (age)	81 (17, 193)	47 (12, 100)
	total population	
BBN	70 (13, 143)	
ISUF	31 (10, 65)

270x135mm (72 x 72 DPI)

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270x135mm (72 x 72 DPI)

254x254mm (72 x 72 DPI)