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A probabilistic model for simultaneous exposure to multiple compounds from food and its use for risk–benefit assessment

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Abstract

A model is presented which allows to quantify the simultaneous distribution of the exposure to two compounds, for example a health-risk and a health promoting compound. The model considers the total dietary intake, and can be used as a first step to study the effects on the balance between risks and benefits following changes in the consumption pattern. The exposure is modelled separately for intake probabilities using a betabinomial model, and for intake amounts using a lognormal model, and these parts are afterwards integrated by Monte Carlo simulation. The model is illustrated using the risk–benefit case of dioxins and the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). High concentrations of both the health adverse compounds and the health promoting compounds are simultaneously present in fatty fish. Calculated exposures were compared with intake limits: the adequate intake for EPA + DHA and the tolerable daily intake (TDI) for dioxins. We estimate the probability that dioxin exposure is below TDI, the probability that EPA + DHA exposure is above the adequate intake, and the probability that both conditions occur simultaneously. We also model the dependence of these probabilities on age.

In the studied population the exposure to both compounds is almost completely below the limits. A scenario study in which meat consumption was replaced by fatty fish consumption shows an increase in the fraction of the population with the recommended intake of EPA + DHA, however also the fraction of the population exceeding the TDI for dioxins is increased. For the example scenario the optimal amount of fatty fish consumption is derived.
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1. Introduction

In many risk–benefit studies regarding the influence of food on health only *average* effects in a population or subgroup are calculated (e.g., Ponce et al., 2000; Wong et al., 2003; Foran et al., 2005; Cox and Popken, 2006). Health effects for individual people may remain unnoticed. Probabilistic modelling of health effects allows answering questions regarding how many people in a population or subgroup can be expected to experience a certain risk or benefit. Or, differently worded, probabilistic models allow to estimate individual *probabilities* to experience

Abbreviations: CPAP, conversion to primary agricultural products; DALY, disability adjusted life years; DHA, docosahexaenoic acid; DNFCS, Dutch National Food Consumption Survey; EAR, estimated average requirement; EPA, eicosapentaenoic acid; TDI, tolerable daily intake; TEF, toxic equivalence factor; TEQ, toxic equivalent; TWI, tolerable weekly intake; PCB, polychlorobiphenyl; PCDF, polychlorinated dibenzofuran; PCDD, polychlorinated dibenzo-*p*-dioxin; RDA, recommended dietary allowance; REML, residual maximum likelihood; WHO, World Health Organization.

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such risks or benefits. This is especially useful when a population is known to have heterogeneous consumption habits.

Risks and benefits from food are often assumed to be caused by specific compounds present in the food. In this paper we focus on chronic risks and benefits related to long-term exposure. For example, omega-3 fatty acids from fish, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are known to reduce the myocardial infarction rate in a population (for a review see, e.g., Marckmann and Grønbæk, 1999), whereas dioxins may have developmental reproductive toxicological and neurotoxic effects (for a review see, e.g., Charnley and Kimbrough, 2006). We approach the risk–benefit case of dioxin and EPA + DHA from a total diet point of view, because other foods than fish are main contributors to dioxin intake.

Both health promoting and hazardous compounds are present in high concentrations in fatty fish such as salmon, eel or herring. Quantitative analysis of both risks and benefits derived from food requires an assessment not only of the exposure to each compound separately, but also of the simultaneous exposure to both compounds.

In this paper we propose a simple statistical model for modelling the joint long-term exposure to both a risk and a health promoting compound. The statistical model has for the univariate case been described in the manual of the Monte Carlo risk assessment program (de Boer and van der Voet, 2006), and it resembles the model proposed by Slob (2006). We here extend the univariate model to two dimensions. These models allow for the possibility that a compound is *not* consumed by a sizeable proportion of the population. For example, people who do not eat fish might have a zero intake of fish fatty acids.

The sensitivity of individuals to substances may also be variable, but in this paper we assume fixed limit values for health effects and concentrate on variability in the chemical exposure. Risk will be equated with the probability of an exposure above (or below) a limit value. This can be seen as a first step to a more complete approach in which also the human sensitivity is modelled in a probabilistic way and in which the health impacts are better quantified.

For illustration, we apply the simultaneous exposure model to available data concerning fish fatty acids and dioxin in the total diet of the Dutch population.

2. Methods

We are interested in the usual (long-term) exposure of a human population to different compounds or compound groups. In this paper we consider a two-dimensional model in order to avoid complexities that arise in still higher dimensions. An example is the simultaneous exposure to dioxins and the omega-3 polyunsaturated fatty acids EPA and DHA, which are all present in fish. In our example we will start from the total toxic equivalent (TEQ) values for dioxin, and the sum of EPA and DHA concentrations.

We want to find the simultaneous distribution in order to quantify the probabilities that the long-term exposures are above or below specified limit values. In the risk–benefit fish example P [dioxin exposure < dioxin limit, EPA + DHA exposure > EPA + DHA limit] would be the probability for the desired situation.

In general, let us consider compounds A and B which may be present or absent in the daily diet. Daily diets are available for N persons on D days (assumed to be representative of both populations of persons and of days). Because we are interested in long-term intake, we just use the average concentration values for compounds A and B to transform food consumption amounts (e.g., 100 g meat) to compound intake amounts (e.g., 14 mg dioxin and 2 mg EPA + DHA). Food consumptions and therefore also intake amounts are further standardized by dividing by body weight. This is common in risk assessment, but not in the assessment of benefits. However, from a methodological point of view there seems to be no reason to keep this distinction, and therefore we apply the body weight standardization throughout.

2.1. Intake probabilities

We assume that each individual person has a fixed probability of intake of compound A, denoted by p_A. For example, a person with $p_A = 0.25$ has intake of compound A once in every four days on average. We use the convention that a small letter indicated the absence of the corresponding compound, so that p_a denotes the probability of no intake of A, and thus $p_a = 1 - p_A$.

Following standard statistical practice for modelling inter-individual variability of probabilities (see, e.g., Slob, 2006) we assume that p_A varies among persons according to a Beta distribution:

$$p_A \sim \text{Beta}(\pi_A, \varphi_A), \tag{1}$$

where the parameter π_A is the average probability of intake in the population, and the parameter φ_A describes the variability between persons. For each person the number of days with a positive intake can be seen as a random variable with a binomial distribution characterized by the parameter p_A. The parameters π_A and φ_A can be estimated by fitting a beta-binomial model to the dataset containing for N persons the number of days with positive intake of A.

For fitting the parameters of the beta-binomial model by maximum likelihood estimation the freely available procedure RBETABINOMIAL (Goedhart, 2006) written for the statistical program Genstat was used.

We consider the intake of compound B conditional on whether or not there is also an intake of compound A. Thus, we define $p_{B|A}$ as the probability of B intake given that there is A intake, and $p_{B|a}$ as the probability of B intake given that there is no A intake. Also these probabilities are allowed to vary among persons in the population according to Beta distributions:

$$p_{B|A} \sim \text{Beta}\left(\pi_{B|A}, \varphi_{B|A}\right), \tag{2}$$

$$p_{B|a} \sim \text{Beta}\left(\pi_{B|a}, \varphi_{B|a}\right). \tag{3}$$

Parameters of these distributions can be estimated by fitting beta-binomial models to datasets restricted to the person-day combinations where A was present or absent, respectively. A special case (appropriate for the dioxin/EPA + DHA example) is when compound B (EPA + DHA) can only occur in combination with compound A (dioxin), for example because all food products containing B (e.g., fish, chicken, eggs) are also known to contain A. In such cases only $p_{B|A}$ is modelled as described above, and $p_{B|a} = 0$ for all persons.

Note: there are alternative ways to model bivariate intake probabilities, e.g., in terms of individual combination probabilities $\{p_{AB}, p_{Ab}, p_{aB}\}$ or joint plus marginal probabilities $\{p_{AB}, p_A, p_B\}$. The advantage of the chosen combination of marginal A plus conditional B probabilities $\{p_A, p_{B|A}, p_{B|a}\}$ is that it guarantees a set of probabilities $p_{AB} + p_{Ab} + p_{aB} + p_{ab}$

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