Generalized method for modeling dose-response relations – application to BENERIS project

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The BENERIS project focuses on the analysis of health benefits and risks associated with food consumption. It aims to develop a comprehensive method that combines both the dose-response modeling and a user-friendly graphical model interface.

Fish consumption is the first case study in the BENERIS project. Relations between levels of contaminants and nutrients contained in fish, personal covariates and impacted various beneficial and adverse health effects are represented via mathematical functions and visualized as directed arrows pointing from one set of nodes to another in a Bayesian Belief Network (BBN). These relations, commonly called dose-response relations, are not explicitly known for health endpoints chosen for this case study, therefore a generalized approach that allows their evaluation and quantification has been proposed. Roughly, the idea is to approximate the (transformed) response variable associated with a certain health effect (which is some function of doses of various substances and personal covariates) by a polynomial function with a finite number of terms using a Taylor series expansion, and then to assess the unknown parameters of this approximation. Unfortunately, even the data on relationships between individual fish constituents and related health endpoints for this case study is very limited. It is hoped that a high level model, such as that proposed here, will guide the overall data collection effort, showing places where effort can best be focused. Where no data can be obtained within the time frame of this project, we may have recourse to structured expert judgment.

This note contains the summary of the generalized method for modeling dose-response relations and presents its application to the fish case study in the BENERIS project. First, a brief description of the method is provided. Then, the means in which the structured expert judgment can be used to estimate parameters of Taylor expansion is explained. Finally, the example of application of the generalized method to the fish case study is demonstrated.

Taylor approximation of unknown dose-response relation

The generalized approach for modeling an unknown dose-response relation using Taylor series has been presented and extensively described in a separate document. In this section only the crucial aspects of this approach are recalled[1].

Let $g(P)$ be an unknown dose-response relation where P denotes the response variable associated with a given health effect. In the context of risk, P is often identified

[1] The more detailed technical report is available from the authors upon request.

with the percentage of individuals in a population experiencing given health effect[2] or simply with probability of the response[3]. However, *P* can be also defined as the size of a health effect.

Health endpoints related to food consumption are influenced by various parameters such as doses (daily or yearly intakes) of food constituents and personal factors (e.g. smoking status, socioeconomic level, age). Let us denote these parameters as $x_1, x_2, \ldots, x_n$ and assume that all of them take values in a continuous range.

Under certain regularity conditions the function $g(P) = f(x_1, x_2, \ldots, x_n)$ at point $x^0 = (x_1^0, x_2^0, \ldots, x_n^0)$ may be approximated as a Taylor expansion:

$$g(P) = f(x_1, x_2, \ldots, x_n) \approx f(x^0) + \sum_{i=1}^{n} f_i^{(1)}(x^0) \cdot (x_i - x_i^0) + \sum_{i=1}^{n} \frac{f_i^{(2)}(x^0)}{2!} \cdot (x_i - x_i^0)^2 + \\ + \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} f_{ij}^{(2)}(x^0) \cdot (x_i - x_i^0) \cdot (x_j - x_j^0) + HOT \tag{1}$$

where *n!* is the factorial of *n*, $f^{(r)}_{\mathrm{var}iables}(x^0)$ denotes the r[th] partial derivative of function *f* with respect to *variables* evaluated at x^0 and x^0 is the vector of average or baseline values of variables $x_1, x_2, \ldots, x_n$, and *HOT* denotes Higher Order Terms. Variables $x_1, x_2, \ldots, x_n$ in (1) may represent either the true variables in the analysis or their transformations.

One can observe that the values of the response variable *P* depend both on the values of predictor variables $x_1, x_2, \ldots, x_n$, their baseline levels and the transformation function *g*. The transformation *g* is chosen to capture the behavior of *P* in low order terms. When *P* represents probability the following forms of *g* are commonly used: $g(P) = ln(P)$ and $g(P) = ln\left(\frac{P}{1-P}\right)$. The second transform is preferred here, as it forms a bijection between the unit interval into the real line, and this means that increments and decrements of dose cannot produce *P* values outside the unit interval.

For the initial approximation, we exclude the quadratic terms from the expansion (1). Then, the approximation of $g(P)$ is just

$$g(P) \approx f(x^0) + \sum_{i=1}^{n} f_i^{(1)}(x^0) \cdot (x_i - x_i^0) + \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} f_{ij}^{(2)}(x^0) \cdot (x_i - x_i^0) \cdot (x_j - x_j^0) \tag{2}$$

Thus, the Taylor expansion of an unknown dose-response relation *f* allows for representing the transformed response variable $g(P)$ as the sum of linear terms and cross-product terms. The model equation with only linear terms is simply an additive model, while the model containing cross-product terms suggests interactions among model

[2] Most often one says about the risk to total population. However, one can be also interested is estimating health effects to specific sub-groups of people in that population (e.g. age groups or sensitive groups).
[3] In the simples case function g(·) in an identity function. But, there are also other choices possible.

variables. However, to decide whether the dose-response relation is linear and whether interactions are possible requires deep knowledge about the case study under investigation.

Although the baseline levels of model variables $x_1, x_2, \ldots, x_n$ might be known (from existing data), for the dose-response relation (2) to be fully specified it is necessary to estimate parameters appearing in its Taylor approximation which are: the zero-order term $f(x^0)$ and (mixed) partial derivatives of f evaluated at point x^0. The values of these parameters could be extracted from data, if such data exists. Otherwise, one can select a group of competent experts and elicit these parameters from them. The method that allows for aggregation of experts' answers into single estimate of variables of interest is the structured expert judgment (Cooke, 1991).

The means by which the parameters of Taylor expansion can be elicited from experts together with few examples of elicitation questions are presented in the next section.

Structured expert judgment and unknown dose-response relationship

Our goal is to estimate all unknown parameters of the dose-response relation represented by the Taylor approximation (2) using structured expert judgment. To achieve this goal we use the following interpretations of the zero-, first- and second-order terms:

- $f(x^0)$ is the background value of $g(P)$ when all variables are equal to their baseline values, i.e. $f(x^0) = g(P_0)$,
- $f_i^{(1)}(x^0)$ denotes the rate of change, relative to the background, in values of $g(P)$ per unit change in variable x_i when the other variables are held constant (at the baseline level),
- $f_{ij}^{(2)}(x^0)$ denotes the rate of change, relative to the background, in values of $g(P)$ per unit change in variables x_i and x_j when the other variables are held constant (at the baseline level).

The (mixed) partial derivatives can be approximated as

$$f_i^{(1)}(x^0) \approx \frac{f(x_1^0, x_2^0, \ldots, x_i^0 + \Delta x_i, \ldots, x_n^0) - f(x_1^0, x_2^0, \ldots, x_n^0)}{\Delta x_i}$$

$$f_{ij}^{(2)}(x^0) \approx \frac{f(x_1^0, x_2^0, \ldots, x_i^0 + \Delta x_i, x_j^0 + \Delta x_j, \ldots, x_n^0) - f(x_1^0, x_2^0, \ldots, x_i^0 + \Delta x_i, x_j^0, \ldots, x_n^0)}{\Delta x_i \cdot \Delta x_j} -$$

$$- \frac{f(x_1^0, x_2^0, \ldots, x_i^0, x_j^0 + \Delta x_j \ldots, x_n^0) - f(x_1^0, x_2^0, \ldots, x_i^0, x_j^0, \ldots, x_n^0)}{\Delta x_i \cdot \Delta x_j}$$

where Δx_i and Δx_j are the increases in values of variables x_i and x_j, respectively ($i, j = 1, 2, \ldots, n; i \neq j$).

Since P depends on levels of x_i ($i = 1, 2, \ldots, n$) one can equivalently write

$$f(x^0) = g(P(x_1^0, x_2^0, \ldots, x_n^0)) \tag{3}$$

$$f_i^{(1)}(x^0) \approx \frac{g(P(x_1^0, x_2^0, \ldots, x_i^0 + \Delta x_i, \ldots, x_n^0)) - g(P(x_1^0, x_2^0, \ldots, x_n^0))}{\Delta x_i} \tag{4}$$

$$f_{ij}^{(2)}(x^0) \approx \frac{g(P(x_1^0, x_2^0, \ldots, x_i^0 + \Delta x_i, x_j^0 + \Delta x_j, \ldots, x_n^0)) - g(P(x_1^0, x_2^0, \ldots, x_i^0 + \Delta x_i, x_j^0, \ldots, x_n^0))}{\Delta x_i \cdot \Delta x_j} -$$

$$- \frac{g(P(x_1^0, x_2^0, \ldots, x_i^0, x_j^0 + \Delta x_j \ldots, x_n^0)) - g((x_1^0, x_2^0, \ldots, x_i^0, x_j^0, \ldots, x_n^0))}{\Delta x_i \cdot \Delta x_j} \tag{5}$$

Below we present the main steps leading to estimating partial derivatives given by equations (4) and (5) and we sketch questions to be asked of the experts[4]. The questions, however, must correspond to quantities that are measurable (observable) and familiar to experts. Thus, the most natural solution is to ask questions related to probability P.

Let assume that function $g(P)$ is known. We start with the zero-order term. Its value can be estimated as a transformation of the baseline response P via function g, where the baseline response is the value of the response variable observed at the baseline levels of variables $x_1, x_2, \ldots, x_n$ or simply $P(x_1^0, x_2^0, \ldots, x_n^0)$.

The baseline response P can be either estimated from existing data or elicited from experts. However, to ask experts about $P(x_1^0, x_2^0, \ldots, x_n^0)$ we have to know the baseline levels of predictor variables $x_1, x_2, \ldots, x_n$. This information may come from various sources, e.g. related studies, toxicology or epidemiological studies. Once the baseline levels of variables $x_1, x_2, \ldots, x_n$ are specified the question to be asked could be formulated as follows

"Suppose that the baseline values of predictor variables are $x_1^0, x_2^0, \ldots, x_n^0$*, respectively. What are the 5%, 50% and 95% quantiles of your subjective probability distribution for the response variable P at values* $x_1^0, x_2^0, \ldots, x_n^0$*?"*

If the value of the zero-order term is known one can formulate questions necessary to assess partial derivatives of first order given by (4). We will ask each expert the following question

[4] Here, only the general type of questions is presented. Once the health effect and the response variable P will be defined more precisely the form of questions will be formulated explicitly.

"Suppose that at the baseline level of variables x_1, x_2, ..., x_n, the baseline response $P(x_1^0, x_2^0, \ldots, x_n^0)$ *is* P^0*. Now, if variable x_i increases by one unit and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in* P^0*, i.e. the number z such that* $P(x_1, x_2, \ldots, x_n) = P(x_1^0, x_2^0, \ldots, x_n^0) + z \cdot P(x_1^0, x_2^0, \ldots, x_n^0)$ *?"*

Combined experts' answers to this question together with the information about the baseline response $P(x_1^0, x_2^0, \ldots, x_n^0)$ will provide the estimate of quantiles of distribution of $P(x_1^0, x_2^0, \ldots, x_i^0 + \Delta x_i, \ldots, x_n^0)$ for variable x_i when $\Delta x_i = 1$ (of course, one could choose other value for Δx_i). We will ask this question n times, as to obtain quantiles of distribution of $P(x_1^0, x_2^0, \ldots, x_i^0 + \Delta x_i, \ldots, x_n^0)$ for each i, $i = 1, 2, \ldots, n$. Then, we will use these results in (3) to estimate the uncertainty distributions of $f_i^{(1)}(x^0)$, $i = 1, 2, \ldots, n$.

Similar procedure will be applied to find the uncertainty distributions of $f_{ij}^{(2)}(x^0)$ for $i \neq j$; $i, j = 1, 2, \ldots, n$. According to (5) we will make use of results obtained for partial derivative of order one $f_i^{(1)}(x^0)$, but we will also ask experts additional question of following form

"Suppose that at the baseline level of variables x_1, x_2, ..., x_n the baseline response $P(x_1^0, x_2^0, \ldots, x_n^0)$ *is* P^0*. Now, if variable x_i increases by one unit AND ALSO variable x_j increases by one unit, but other variables remain unchanged (at the baseline levels), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in* P^0*, i.e. the number z such that* $P(x_1, x_2, \ldots, x_n) = P(x_1^0, x_2^0, \ldots, x_n^0) + z \cdot P(x_1^0, x_2^0, \ldots, x_n^0)$ *?"*

Aggregation of experts' estimates on this question together with information about baseline response will give us three quantile points of distribution of $P(x_1^0, x_2^0, \ldots, x_i^0 + \Delta x_i, x_j^0 + \Delta x_j, \ldots, x_n^0)$ for $\Delta x_i = \Delta x_j = 1$, $i \neq j$; $i, j = 1, 2, \ldots, n$. As before this question will be asked for each pair of distinct variables. Finally, the uncertainty distribution of $f_{ij}^{(2)}(x^0)$, for each $i \neq j$; $i, j = 1, 2, \ldots, n$ will be obtained by substitution of all data provided into (5).

One can notice that if the response variable P represents probability then the answers to the last two questions presented above provide quantiles of the probability distributions of relative risks.

The generalized method for modeling dose-response relations is valid only when all predictor variables take values on a continuous scale. However, some of these variables may be categorical (also called nominal or discrete), that is they can posses different states. Separate dose-response relations will be evaluated for each state of categorical variable according to the generalized method, quantified and then combined.

The next section of this note is meant to illustrate the application of generalized method presented above to the fish case study in the BENERIS project. It provides the description of variables in the case study including predictor and response variables and contains the general forms of all possible dose-response relations.

Illustrative example – simpler BBN model in the BENERS project

In this section the BBN model for the fish case study in the BENERIS project is described. Information presented here is based on discussions among project participants held in Kuopio in December 2006 and supported by recent comments of Jouni Tuomisto[5].

Recalling, the main goal of the BENERIS project is to estimate the health effects in a specified population as a result of exposure to various contaminants and nutrients through ingestion of fish. The population, however, consists of subpopulations - more or less susceptible subgroups of people. Roughly, these subgroups are age groups and gender groups. Distinction between these subgroups is very important when calculating health effects since not all people in a population are exposed to the same levels of contaminants and nutrients and not all of them will respond in the same quantitative manner to the same dose. For that reason we decided to divide the population into four age groups

$$\text{I} = (0, 5\text{yr}),\ \text{II} = (6, 15\text{yr}),\ \text{III} = (16, 50\text{yr}),\ \text{IV} = (51+\text{yr})$$

and for each group we assigned different probability distributions of yearly intakes of nutrients and chemicals contained in fish. The fish constituents of interest are:

- dioxins and furans (*D*),
- polychlorinated biphenyls (*PCB*),
- methyl mercury and selenium (*MeHg*),
- fish oils (*F*).

The yearly intakes of two first groups of contaminants are expressed in nanograms per kilogram body mass, the yearly intake of the methyl mercury and selenium is given in micrograms per kilogram body mass, while the yearly intake of the last substance is gram per kilogram body mass.

Moreover, personal factors such as smoking (*SM*) and socioeconomic status (*SES*) are also taken into account. Smoking status is specific for each single age group and is measured as yearly intake of nicotine during smoking and passive smoking while the socioeconomic status is a global parameter (common for all age groups) which is measured by the proxy variable ‘years of schooling received, or to be received’. This variable serves as an indicator of health awareness, ability to access quality health care, attention to diet, etc.

The first age group is a very important group. It includes newborn children who in fact are exposed during pregnancy and nursing period to various fish constituents and

[5] Jouni Tuomisto provided comments on the methodology for estimating the dose-response relations of various endpoints in the fish case study. These comments are available at the BENERIS website.

nicotine the mother is exposed to. For that reason, for the first age group data on the yearly intakes of substances mentioned should take into account intakes from these two exposure routes.

The health endpoints resulting from exposure to fish constituents are:

- cancer,
- developmental effects,
- learning disability,
- cardiovascular disease.

In this study example, these health effects are defined in terms of remaining lifetime risks. That is, cancer is defined as the remaining lifetime risk of developing cancer and similarly cardiovascular disease, developmental defects (e.g. dental effects) and learning disability - as remaining lifetime risks of having cardiovascular disease, developmental defects and learning disability, respectively. Learning disability, however, is a more specific health effect. In general this health effect is said to occur when person's IQ score is higher or lower than the average IQ in a group of people this person belongs to (e.g. age group). Thus, learning disability is not expressed in terms of probability of occurrence of a health effect, but rather as the size of the effect measured as a change in IQ score.

However, not all health effects considered in the fish case study are estimated based on lifetime exposure. That is, the developmental effects and learning disability are mainly influenced by exposure to substances in *utero*, infancy, childhood and adolescence (in age periods I and II) while cancer and cardiovascular disease depend on the lifetime exposure. Moreover, all health effects mentioned may be considered not only with respect to age groups but also with respect to gender. This is the case especially for certain cancer sites (e.g. breast, prostate) and developmental defects, but we omit this here and assume that the risks of health effects are the same for males and females.

These remarks imply that the existing BBN model for the fish case study in the BENERIS project should be changed. The modified general form of BBN model is shown below where the red arrows represent new arcs.

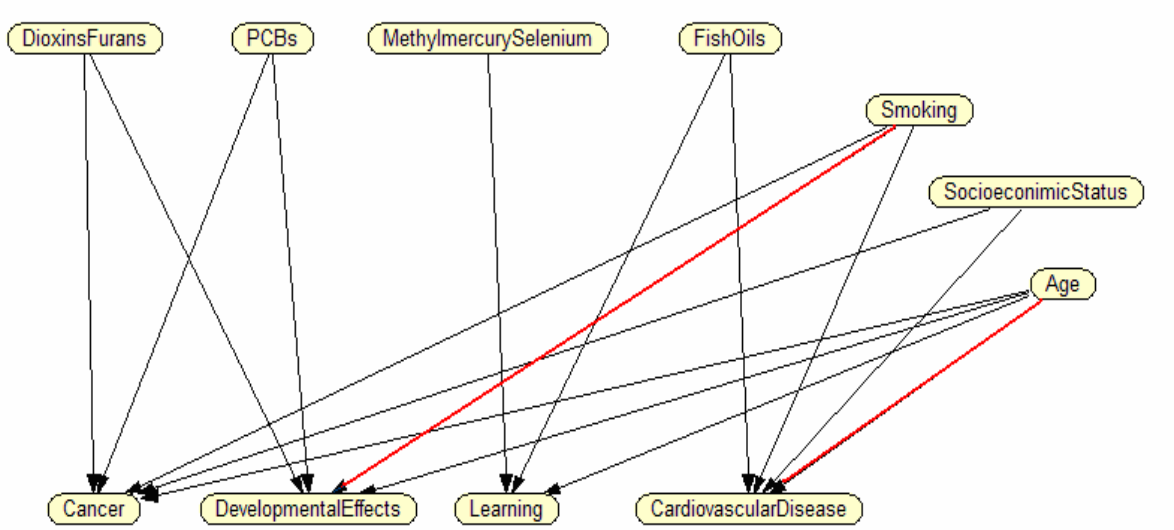

Figure 1: Modified Fish Consumption BBN

One can see that the arrow between smoking status and developmental effects was added. This is because mother's smoking is possible to cause some of the developmental defects[6].

Our goal is to provide and quantify the dose-response relationships for each *endpoint* variable (sink nodes of BBN) with regard to its relevant *effector variables* (source nodes of BBN) using the generalized method and the structured expert judgment as described in previous sections of this note. Below we discuss and present the general forms of these relations.

Since we divide members of the population according to age the dose-response relations are provided and the health effects are estimated for each age group separately. Let D_i, PCB_i, $MeHg_i$, F_i, SM_i be respectively the yearly intakes (per kilogram body mass) of dioxins and furans, PCBs, methyl mercury and selenium, fish oils and nicotine for i^{th} age group, where i = I, II, III, IV and let SES represents the socioeconomic status. Thus, we can represent the dose-response relations for age group i as follows

$g(pC_i) = f(D_i, PCB_i, SM_i, SES)$, i = I, II, III, IV,

$g(pD_i) = d(D_i, PCB_i, SM_i)$, i = I, II,

$L_i = c(MeHg_i, F_i)$, i = I, II,

$g(pCVD_i) = k(F_i, SM_i, SES)$, i = I, II, III, IV,

where:

- pC_i is the lifetime risk of developing cancer for people in age group i,

[6] See comments added to the "Dose-response functions of various endpoints due to fish exposure" placed at the BENERIS website.

- pD_i is the lifetime risk of developmental effects for people in age group i,
- L_i is the change in IQ score for people in age group i,
- $pCVD_i$ is the lifetime risk of getting cardiovascular disease for people in age group i,
- g is the transformation function $g(P) = ln\left(\frac{P}{1-P}\right)$,
- f, d, c and k are the Taylor approximations of the transformed response variables.

In order to fully specify approximations of the dose-response relations using Taylor argument we have to determine which linear terms and interaction terms are possible.

In case of cancer the intake of dioxins and furans, PCBs and nicotine increase the lifetime risk of developing cancer. Moreover, socioeconomic status may interact with the intake of dioxins and furans, PCBs and nicotine while the intake of nicotine may interact with intakes of dioxins and furans.

For developmental defects intakes of dioxins and furans, PCBs and nicotine increase the risk, but also interactions between intake of nicotine and intakes of two other groups of substances are possible.

The IQ score may decrease due to intake methyl mercury and selenium, but the intake of fish oils may raise this score.

Finally, socioeconomic status and the intake of fish oils have a decreasing effect on the lifetime risk of cardiovascular disease in general, and these variables may interact with each other as well.

It must be noted that the health endpoints considered in the fish case study (and of course many others) strictly depend not only on the exposure dose per unit time (per kg body mass), but also on the exposure duration. The product of these two factors provides a total dose over the age period or simply a cumulated dose which administrated in the human body leads to more or less severe effect (except cancer) and greater or smaller risk of that effect. Since we split the population into age groups and we provide the dose-response relations for each of them separately, the exposure periods and thus cumulated doses for these groups are different. We assume that the exposure period for each age group is equal to the number of years this group includes and amounts for 5, 10, 34 and 24 respectively for age group I, II, III and IV[7]. So, for example, if we estimate the remaining lifetime risk of developmental effects for a person in age group II (from 6 to 15yr), we assume that this person is exposed to dose D_{II} over a period of 10 years (until he/she reaches the age of 16). However, we do not exclude the fact that this person could be exposed to dioxins and furans when he/she was in age group I, but we simply don't count how large this exposure was.

Hence, the Taylor approximations of the dose-response relations are given by the following expressions:

[7] We assumed that the average lifetime in the population is 75 years.

$$ln\left(\frac{pC_i}{1-pC_i}\right) = f_0 + f_1^i \cdot t_i \cdot (D_i - D_i^0) + f_2^i \cdot t_i \cdot (PCB_i - PCB_i^0) + f_3^i \cdot t_i \cdot (SM_i - SM_i^0) +$$

$$+ f_4^i \cdot (SES - SES^0) + f_{13}^i \cdot (t_i)^2 \cdot (D_i - D_i^0) \cdot (SM_i - SM_i^0) + f_{14}^i \cdot t_i \cdot (D_i - D_i^0) \cdot (SES - SES^0) + \quad (6)$$

$$+ f_{24}^i \cdot t_i \cdot (PCB_i - PCB_i^0) \cdot (SES - SES^0) + f_{34}^i \cdot t_i \cdot (SM_i - SM_i^0) \cdot (SES - SES^0)$$

$$ln\left(\frac{pD_i}{1-pD_i}\right) = d_0 + d_1^i \cdot t_i \cdot (D_i - D_i^0) + d_2^i \cdot t_i \cdot (PCB_i - PCB_i^0) + d_3^i \cdot t_i \cdot (SM_i - SM_i^0) +$$

$$+ d_{13}^i \cdot (t_i)^2 \cdot (D_i - D_i^0) \cdot (SM_i - SM_i^0) + d_{23}^i \cdot (t_i)^2 \cdot (PCB_i - PCB_i^0) \cdot (SM_i - SM_i^0) \quad (7)$$

$$L_i = c_0 + c_1^i \cdot t_i \cdot (MeHg_i - MeHg_i^0) + c_2^i \cdot t_i \cdot (F_i - F_i^0) \quad (8)$$

$$ln\left(\frac{pCVD_i}{1-pCVD_i}\right) = k_0 + k_1^i \cdot t_i \cdot (F_i - F_i^0) + k_2^i \cdot t_i \cdot (SM_i - SM_i^0) + k_3^i \cdot (SES - SES^0) +$$

$$+ k_{12}^i \cdot (t_i)^2 \cdot (F_i - F_i^0) \cdot (SM_i - SM_i^0) + k_{13}^i \cdot t_i \cdot (F_i - F_i^0) \cdot (SES - SES^0) + \quad (9)$$

$$+ k_{23}^i \cdot t_i \cdot (SM_i - SM_i^0) \cdot (SES - SES^0)$$

where

- i is the indicator of the age group,
- t_i is the exposure period for age group i,
- $f_{variables}^i$ are the partial derivatives of $g(pC_i)$ evaluated at baseline values of D, PCB, SM and SES for age group i (SES is a global parameter),
- $d_{variables}^i$ are the partial derivatives of $g(pD_i)$ evaluated at baseline values of D, PCB, SM for age group i,
- $c_{variables}^i$ are the partial derivatives of L_i evaluated at baseline values of $MeHg$ and F for age group i,
- $k_{variables}^i$ are the partial derivatives of $g(pCVD_i)$ evaluated at baseline values of F, SM and SES for age group i (SES is a global parameter).

One can observe that the zero-order terms in equations (6) – (9) are not indexed by i. This is because we assume that the baseline response of each health effect considered here is the same among all age groups or in other words the baseline response is population-

specific. Moreover, in case of learning disability we assume that for the baseline levels of all input variables the IQ score does not change and hence c_0 is in equation (8) is 0.

Since approximations of the dose-response relations are already known the last step leading to quantitative estimates of health effects related to fish consumption is assessment of partial derivatives appearing in these approximations. As stated before the structured expert judgment is used for that purpose. The set of questions concerning given health effect in a certain age group has been prepared and is placed as a supplement at the end of this note.

The generalized method based on Taylor series not only has been described in context of the fish case study in the BENERIS project but it also has been applied in reality. Next section of this note contains a brief description of this application.

Model emulator

Based on information concerning the fish case study in the BENERIS project provided in the previous section, a model emulator has been prepared. That is, we have created and fully quantified a BBN model that imitates the real BBN model for this case study. The functional relations between effector variables and endpoints are emulated as probabilistic dependences, expressed as conditional rank correlations. The model is non-realistic in the sense that the input data is fictitious[8]. To create the model emulator, two tools were used: an uncertainty program *Unicorn* and the continuous BBN software *UniNet*. The main steps according to which this model has been created are summarized below:

1. Characterization of source nodes of the BBN model. This step covers:

   - determination of the percent of people in each of four age groups,
   - assignment of probability distributions of the yearly intakes of all fish constituents listed on page 6 and the yearly intake of nicotine,
   - assignment of probability distribution of socioeconomic status which is a global parameter in the model,
   - setting constant values for the zero-order terms and partial derivatives appearing in Taylor approximations of the dose-response relations of health endpoints in the fish case study.

2. Introduction of the functional relations between source and sink nodes (health endpoints) of the BBN model. In this step Taylor approximations of the dose-response relations are used.

The information provided in the two first steps is coded in an uncertainty program *Unicorn*.

3. Generation of a very large sample file based on information provided in previous steps. *Unicorn* program is used for that purpose.

[8] The data on the yearly intakes of source nodes of the BBN has been provided (where possible) based on literature.

4. Importing the sample file in *UniNet*.

5. Construction of the BBN model. Once the sample file is imported in *UniNet* the user can create the BBN using source and sink nodes of the real model. The program assigns the probability distributions for all nodes in the BBN and quantifies arcs of this BBN based on sample file.

6. Conditionalization (Inference). Once the BBN is created, conditioning can be performed. This means that one can enter available observations in the BBN, update the entire structure and observe changes within the model.

The last two steps presented above are partially based on the normal-copula-vine approach for continuous Bayesian Belief Networks. According to this approach the arcs of the BBN are associated with (conditional) rank correlations calculated from the sample file which are further used in conditionalization. Since the normal-copula-vine method is based on the theory of multivariate Gaussian distribution the conditioning in *UniNet* proceeds analytically.

Figure 2 shows the BBN for the fish case study with nodes represented as histograms. These reflect user-input distributions on the intake of the effector variables per age group, and the distributions of personal effector variables.

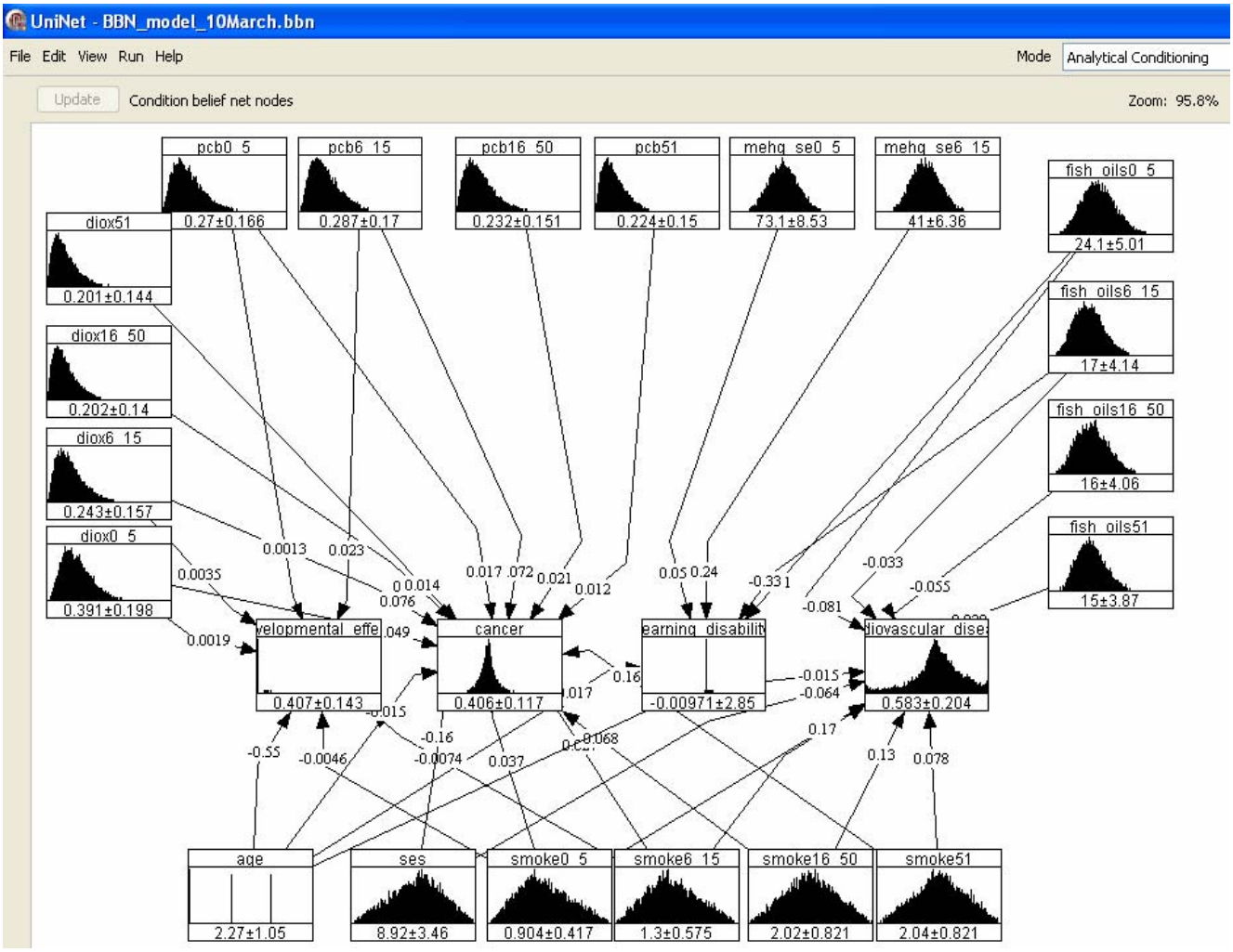

Figure 2: BBN with Histograms

The model emulator supports analytical conditioning. The user can conditionalize any variable on a specific value and view the conditional distribution. Figure 3 shows the conditionalization on very high intake of dioxins and PCBs after age 16, heavy smoking and low socioeconomic status. Not the strong increase in the probability of cardiovascular disease and the increase in cancer risk. It must be emphasized that the quantification of this BBN is merely illustrative, not realistic. It is designed to show how the BBN can be used in decision support.

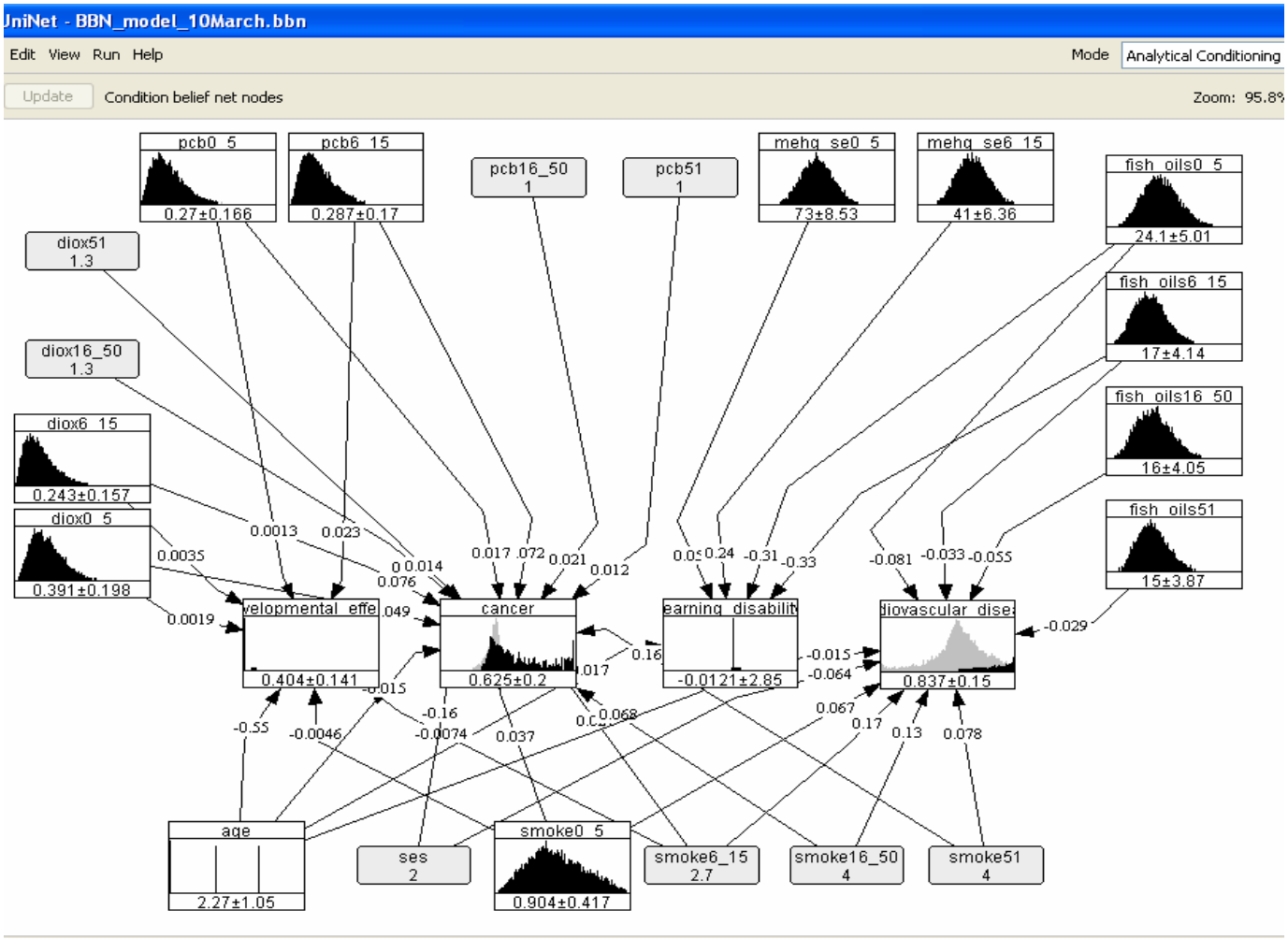

Figure 3: Conditional BBN

Conclusions

We believe that the generalized method for modeling dose-response relations is promising. However, to gain insight into problems that may arise during application of this method, real-life data is required. Hence, our future work will be focused on making the BBN model for the fish case study in the BENERIS project more realistic. We will try to gain as much reliable data as possible and elicit from experts the unknown parameters of Taylor approximation of the dose-relations.

We will concentrate our effort on software development. We are working on a BBN that supports sample-based conditioning as well as analytic conditioning. When this is accomplished, the influence of the effector variables on the endpoints that is captured in conditionalization will be the true functional relations and not probabilistic emulations of functional relations.

Questionnaire

Case 1. Cancer dose-response relationship as a function of the yearly intake of dioxins and furans, the yearly intake of PBCs, the yearly intake of nicotine and socioeconomic status

Population-specific baseline response:
Consider an infinite population of males and females who are characterized by socioeconomic status, who are exposed to dioxins and furans, and PCBs via ingestion of fish and exposed to nicotine via cigarette smoke. What are the 5%, 50% and 95% quantiles of your subjective probability distribution for the baseline lifetime probability of developing cancer in this population?

Age group I
Consider the subgroup of people of that population between 0 and 5 years of age in which the baseline values of the yearly intake of dioxins and furans, the yearly intake of PCBs, the yearly intake of nicotine and the number of passed school years are D_I, PCB_I, SM_I, SES, respectively. Please answer the following questions:

1. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled (form the baseline level) and other variables remain unchanged, what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

2. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of PCBs is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

3. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

4. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

5. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

6. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

7. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of PCBs is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

8. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of nicotine increases by one unit and also the baseline number of school years passed by a member of this subgroup increases by one unit and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

Age group II

Consider the subgroup of people in that population between 6 and 15 years of age in which the baseline values of the yearly intake of dioxins and furans, the yearly intake of PCBs, the yearly intake of nicotine and the number of passed school years are D_{II}, PCB_{II}, SM_{II}, SES, respectively. Please answer the following questions:

1. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled (form the baseline level) and other variables remain unchanged, what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

2. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of PCBs is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

3. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

4. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

5. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

6. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

7. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of PCBs is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

8. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of nicotine increases by one unit and also the baseline

number of school years passed by a member of this subgroup increases by one unit and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

Age group III

Consider the subgroup of people of that population between 16 and 50 years of age in which the baseline values of the yearly intake of dioxins and furans, the yearly intake of PCBs, the yearly intake of nicotine and the number of passed school years are D_{III}, PCB_{III}, SM_{III}, SES, respectively. Please answer the following questions:

1. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled (form the baseline level) and other variables remain unchanged, what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

2. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of PCBs is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

3. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?"

4. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

5. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

6. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

7. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of PCBs is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

8. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of nicotine increases by one unit and also the baseline number of school years passed by a member of this subgroup increases by one unit and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

Age group IV

Consider the subgroup of people of that population in age of 51 years and older in which the baseline values of the yearly intake of dioxins and furans, the yearly intake of PCBs, the yearly intake of nicotine and the number of passed school years are D_{IV}, PCB_{IV}, SM_{IV}, SES, respectively. Please answer the following questions:

1. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled (form the baseline level) and other variables remain unchanged, what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

2. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of PCBs is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

3. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your

subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

4. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

5. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

6. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

7. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of PCBs is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

8. Suppose that the baseline lifetime probability of developing cancer is pC_0. Now, if the baseline level of the yearly intake of nicotine increases by one unit and also the baseline number of school years passed by a member of this subgroup increases by one unit and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of cancer in the remaining lifetime, i.e. the number z such that *Prob. Cancer in Remaining Life* = $pC_0 + z \cdot pC_0$?

Case 2. Dose-response relationship for developmental effects as a function of the yearly intake of dioxins and furans, the yearly intake of PCBs and the yearly intake of nicotine

Population-specific baseline response:
Consider an infinite population of males and females who are exposed to dioxins and furans, and PCBs via ingestion of fish and exposed to nicotine via cigarette smoke. What is the estimate of the 5%, 50% and 95% quantiles of your subjective probability distribution for the baseline probability of having developmental effects in this population?

Age group I
Consider the subgroup of people of that population between 0 and 5 years of age in which the baseline values of the yearly intake of dioxins and furans, the yearly intake of PCBs and the yearly intake of nicotine D_I, PCB_I, SM_I, respectively. Please answer the following questions:

1. Suppose that the baseline probability of having developmental defects is pD_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of developmental effects i.e. the number z such that *Prob. Dev. Effects* = $pD_0 + z \cdot pD_0$?

2. Suppose that the baseline probability of having developmental defects is pD_0. Now, if the baseline level of the yearly intake of PCBs is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of developmental effects i.e. the number z such that *Prob. Dev. Effects* = $pD_0 + z \cdot pD_0$?

3. Suppose that the baseline probability of having developmental defects is pD_0. Now, if the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of developmental effects i.e. the number z such that *Prob. Dev. Effects* = $pD_0 + z \cdot pD_0$?

4. Suppose that the baseline probability of having developmental defects is pD_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of developmental effects i.e. the number z such that *Prob. Dev. Effects* = $pD_0 + z \cdot pD_0$?

5. Suppose that the baseline probability of having developmental defects is pD_0. Now, if the baseline level of the yearly intake of PCBs is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability

distribution for the percent change in the probability of developmental effects i.e. the number z such that *Prob. Dev. Effects* = $pD_0 + z \cdot pD_0$?

Age group II

Consider the subgroup of people of that population between 6 and 15 years of age in which the baseline values of the yearly intake of dioxins and furans, the yearly intake of PCBs and the yearly intake of nicotine D_{II}, PCB_{II}, SM_{II}, respectively. Please answer the following questions:

1. Suppose that the baseline probability of having developmental defects is pD_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of developmental effects i.e. the number z such that *Prob. Dev. Effects* = $pD_0 + z \cdot pD_0$?

2. Suppose that the baseline probability of having developmental defects is pD_0. Now, if the baseline level of the yearly intake of PCBs is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of developmental effects i.e. the number z such that *Prob. Dev. Effects* = $pD_0 + z \cdot pD_0$?

3. Suppose that the baseline probability of having developmental defects is pD_0. Now, if the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of developmental effects i.e. the number z such that *Prob. Dev. Effects* = $pD_0 + z \cdot pD_0$?

4. Suppose that the baseline probability of having developmental defects is pD_0. Now, if the baseline level of the yearly intake of dioxins and furans is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of developmental effects i.e. the number z such that *Prob. Dev. Effects* = $pD_0 + z \cdot pD_0$?

5. Suppose that the baseline probability of having developmental defects is pD_0. Now, if the baseline level of the yearly intake of PCBs is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of developmental effects i.e. the number z such that *Prob. Dev. Effects* = $pD_0 + z \cdot pD_0$?

Case 3. Dose-response relationship for learning disability as a function of the yearly intake of methyl mercury and selenium and the yearly intake of fish oils

Population-specific baseline response:
Consider an infinite population of males and females who are exposed to methyl mercury and selenium and fish oils via ingestion of fish. Let assume that the baseline change in IQ score in this population is 0.

Age group I
Consider the subgroup of people of that population between 0 and 5 years of age in which the baseline values of the yearly intake of methyl mercury and the yearly intake of fish oils are $MeHg_I$, F_I, respectively. Please answer the following questions:

1. Suppose that the baseline level of the yearly intake of methyl mercury in this subgroup of people is doubled and other variables remain unchanged (at the baseline level). What are the 5%, 50% and 95% quantiles of your subjective probability distribution for the change in IQ score?

2. Suppose that the baseline level of the yearly intake of fish oils in this subgroup of people is doubled and other variables remain unchanged (at the baseline level). What are the 5%, 50% and 95% quantiles of your subjective probability distribution for the change in IQ score?

Age group II
Consider the subgroup of people of that population between 6 and 15 years of age in which the baseline values of the yearly intake of methyl mercury and the yearly intake of fish oils are $MeHg_{II}$, F_{II}, respectively. Please answer the following questions:

1. Suppose that the baseline level of the yearly intake of methyl mercury in this subgroup of people is doubled and other variables remain unchanged (at the baseline level). What are the 5%, 50% and 95% quantiles of your subjective probability distribution for the change in IQ score?

2. Suppose that the baseline level of the yearly intake of fish oils in this subgroup of people is doubled and other variables remain unchanged (at the baseline level). What are the 5%, 50% and 95% quantiles of your subjective probability distribution for the change in IQ score?

Case 4. Dose-response relationship for cardiovascular disease as a function of the yearly intake of fish oils, the yearly intake of nicotine and socioeconomic status

Population-specific baseline response:
Consider an infinite population of males and females who are characterized by socioeconomic status, who are exposed to fish oils via ingestion of fish and exposed to nicotine via cigarette smoke. What is the estimate of the 5%, 50% and 95% quantiles of

your subjective probability distribution for the baseline lifetime probability of getting cardiovascular disease in this population?

Age group I

Consider the subgroup of people of that population between 0 and 5 years of age in which the baseline values of the yearly intake of fish oils, the yearly intake of nicotine and the number of passed school years are F_I, SM_I, SES, respectively. Please answer the following questions:

1. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

2. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

3. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

4. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

5. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

6. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of nicotine is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95%

quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that *Prob. CVD* = $pCVD_0 + z \cdot pCVD_0$?

Age group II

Consider the subgroup of people of that population between 6 and 15 years of age in which the baseline values of the yearly intake of fish oils, the yearly intake of nicotine and the number of passed school years are F_{II}, SM_{II}, SES, respectively. Please answer the following questions:

1. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that *Prob. CVD* = $pCVD_0 + z \cdot pCVD_0$?

2. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that *Prob. CVD* = $pCVD_0 + z \cdot pCVD_0$?

3. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that *Prob. CVD* = $pCVD_0 + z \cdot pCVD_0$?

4. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that *Prob. CVD* = $pCVD_0 + z \cdot pCVD_0$?

5. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that *Prob. CVD* = $pCVD_0 + z \cdot pCVD_0$?

6. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of nicotine is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95%

quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

Age group III

Consider the subgroup of people of that population between 16 and 50 years of age in which the baseline values of the yearly intake of fish oils, the yearly intake of nicotine and the number of passed school years are F_{III}, SM_{III}, SES, respectively. Please answer the following questions:

1. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

2. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

3. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that Prob. CVD = $pCVD_0 + z \cdot pCVD_0$?

4. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

5. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

6. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of nicotine is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95%

quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

Age group IV

Consider the subgroup of people of that population in age of 51 years and older in which the baseline values of the yearly intake of fish oils, the yearly intake of nicotine and the number of passed school years are F_{IV}, SM_{IV}, SES, respectively. Please answer the following questions:

1. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

2. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

3. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

4. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and also the baseline level of the yearly intake of nicotine is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that Prob. CVD = $pCVD_0 + z \cdot pCVD_0$?

5. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of fish oils is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95% quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?

6. Suppose that the baseline lifetime probability of getting cardiovascular disease is $pCVD_0$. Now, if the baseline level of the yearly intake of nicotine is doubled and also the baseline number of school years passed by a member of this subgroup is doubled and other variables remain unchanged (at the baseline level), what are the 5%, 50% and 95%

quantiles of your subjective probability distribution for the percent change in the probability of CVD i.e. the number z such that $Prob.\ CVD = pCVD_0 + z \cdot pCVD_0$?