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Application of Probabilistic Methods in Dietary Risk Assessment

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Abstract

The decisions taken during food control need to be based on scientifically established facts and the analysis of data, in which the role of risk assessment is essential. The four steps in internationally accepted risk assessment scheme are hazard identification, hazard characterization, exposure assessment and risk characterization, with the latter taking into account the former steps. The probabilistic exposure assessment takes into account all possible (food consumption and occurrence) values and the weight of each possible scenario. The approach enables estimation with greater information content, when enough data are available. In my research I applied this approach to national data assessing the deoxynivalenol (DON) intake from white bread consumption, captan intake from apple consumption and cumulative intake of organophosphorous pesticide residues. I focused on the intake assessment of pesticide residues, which is applicable for the intake assessment of other contaminants, too. I verified that probabilistic methods can be applicable without sophisticated computer methods, using our national databases. Using the elaborated methods when enough data are available, the dietary exposure of any food contaminant, food additive or pesticide residue can be characterized and conclusions can be drawn regarding the risk of the Hungarian population.

Keywords: exposure, dietary risk assessment, pesticide residue, food contaminant, probabilistic

Introduction to risk assessment

It is essential that only scientifically sound decisions should be made in food control procedures, in which risk assessment plays a key role. The four internationally accepted steps of food safety risk assessment (IPCS, 1999) are: hazard identification, hazard characterization, exposure (intake) assessment and, based on these, risk characterization. Toxicological evaluation of the potential effects takes place during the phases of the identification and characterization of any specific hazard. This is followed – during the assessment of exposure

– by working out an estimate or estimates of the quantity of the substance with which the hazard is associated that may enter the consumer's body. In the last – risk characterization – phase an assessment is made, on the basis of the preceding three steps and taking uncertainties also into account, of whether the hazard actually causes any health-related risk in the population concerned, and of the affected proportion of the population. In the toxicological characterization phase (Steps 1 and 2) the dose-effect relationship, that is, the extent/severity of the effect to be associated with each of the different doses studied, is usually analyzed on the basis of animal test results. This is when the NOAEL (*no observed adverse effect level,*) is established. Another – more accurate – approach is given by the technique called BMD *(benchmark dose),* in which a dose is specified on the basis of the relations between all of the analyzed doses and effects. On the basis of the NOAEL or the BMD values and in view of the uncertainties associated with the estimate, the ADI (acceptable daily intake, relevant for long term exposure) or TDI (tolerable daily intake, relevant for long term) and/or short term ARfD (acute reference dose, relevant for short term exposure) levels are finally established, as doses whose intake does not entail adverse impacts on human health.

The deterministic and probabilistic approach

Quantitative estimates of dietary exposure involves the combination of food consumption data with data pertaining to the occurrence of a compound, applying a deterministic or an – increasingly widely known – probabilistic technique. The deterministic approach – in which a typical (e.g. average or high percentile) consumption value is multiplied by a chemical residue value – does not factor in the variability and uncertainty of food consumption habits and of contamination levels, as a consequence of which it may, in cases, produce unreasonably extreme results. By contrast, the probabilistic method takes all possible relevant values into account, while weighting the probability of occurrence.

According to a tiered procedure the probabilistic approach may supplement a deterministic estimate by producing an estimate that is closer to the truth as a result of studying distribution patterns (EFSA, 2012). Distribution patterns describe the variability of consumption habits, contaminant concentrations and other relevant parameters, such as intake, making it possible to quantify uncertainty factors. The deterministic approach is, however, easier to carry out and if its result is not indicative of the likelihood of any risk, there is no need for refining it by carrying out a probabilistic procedure as well.

Probabilistic estimates require databases with sufficiently large numbers of samples. The larger the number of data the more information is carried by the estimate made using them. In practice, the procedure may be as follows: One particular day with the relevant consumption data of one specific individual (of a known body weight) has to be selected at random from the consumption database. Every single amount of food (in terms of kg) consumed by the person concerned on that particular day must be multiplied by the contaminant concentration (mg/kg) selected at random, for the given specific kind of food. The concentration data may also be selected from the estimated (adjusted) distribution of the given contaminant's concentrations (parametric technique). The intake figures calculated for each kind of food are aggregated, then divided by the individual's body weight. The process is iterated multiple time using other days' personal consumption data, producing a frequency distribution that reflects the possible combinations of the consumption and contaminant levels. This enables the establishment of the probability of the reference value (e.g. the ARfD) is exceeded by the consumers' intakes as a consequence of the consumption of one or more contaminated food products.

The probabilistic approach makes it possible to produce estimates of increased information content, provided the necessary data are available. This is the approach I adapted in my research to domestic data to establish the characteristics of Hungarian consumers' deoxynivalenol (DON) intake from white bread consumption, captan intake from apple consumption and their cumulative intake of organophosphorous pesticide residues that have an identical mode of action. I worked out the techniques focusing on estimating the intake of pesticide residues. The same techniques can also be used for making estimates of other contaminants as well. For the calculations I used data from the latest nationwide consumption survey (Szeitz-Szabó et al., 2011), and the results of control tests performed by the competent authority, with the help of a MS Excel macro. I demonstrate the application of these methods in practice through the calculation of the Hungarian population's exposure to various types of food contaminants and pesticide residues originating from food consumption.

Deoxynivalenol intake through white bread consumption

Using the so-called parameter-based method – with adequate software support – conclusions can be drawn concerning intake from distribution functions of consumption and occurrence data. The probabilistic technique applied in our case relies on the empirical approach, using all of the available data and random sampling, with replacement, from all of the available data.

DON concentrations measured in 176 wheat flour samples and 1360 bread consumption data (Rodler et al., 2005) were used in working out the estimate. Since wheat flour is consumed in the form of bread, assuming 700 grams of flour as input quantity on the basis of its recipe a processing factor of 0.7 is applied (700g of flour / 1000g of bread). DON being relatively heat-stable, the decrease in its concentration under the impact of heat treatment was not modelled.

Consumption data and the DON concentration data reduced with the processing factor were combined together in two ways. On the one hand, 200,000 samples were taken from each of the databases by random sampling, with replacement, calculating intake by multiplying them by each other. On the other hand, each data of one database were multiplied with each data of the other database, in all possible combinations. The DON intake of domestic consumers from white bread consumption was characterized with the selected percentile values of the resulting distributions. The main percentile values of the calculated intake were summed up in Table 1.

Table 1

Distribution of the DON exposure originating from white bread consumption

Median	0.1–0.15 μg/kgbw
95th percentile	1.0 μg/kgbw
Ratio of exposure over PMTDI	~5%

Source: AMBRUS et al., 2011

The provisional maximum tolerable daily intake (PMTDI) of DON (and its acetylated derivatives) is 1 μg/kgbw (JECFA, 2011). The median of the resulting intake distribution is way below the above level, but at the 95th percentile it reaches the reference value. Accordingly, in approx. 5% of the calculated exposures health risk resulting from DON intake cannot be ruled out.

Estimation of the acute intake of pesticide residues

In estimating acute intake emphasis is laid on the intake of contaminants/pesticide residues originating from food consumed in a large quantity in a short period of time. Intake of large amounts of pesticide residues may occur when one consumes a large quantity of a produce containing a large amount of residue. By agreement, the threshold for the consumption of a large amount is set at the 97.5th percentile of the individual consumptions of the consumers of the product concerned (WHO, 1997). In addition to the above, a variability factor was introduced in order to take into account the variability of the residue concentration across the sample elements (e.g. different apples). By multiplying the sample's average residue concentration with this factor a high residue content – which may be regarded as sufficiently conservative – is taken into account in working out an estimate of the acute intake with the deterministic method.

In developing an intake estimate I used a total of 4720 apple consumption data, captan concentrations measured in 378 apples (2010–2011), 1769 chemical residue variability data and the mass data of 641 apples. I took apple mass samples at random in the applied probabilistic procedure, until their sum became equal to the given day's apple consumption. I assigned one particular, randomly chosen residue value to each apple of that day and different, randomly chosen variability data to these different apples, according to the following equation:

$$ESTI_{nk} = ([R_k \times \upsilon_{i1} \times \mathrm{m}_1] + [R_k \times \upsilon_{i2} \times \mathrm{m}_2] + ...[R_k \times \upsilon_{il} \times \mathrm{m}_L]) / bwkg_n,$$

where *ESTI* is the short term intake, *n* is the day of consumption, R_k is the average chemical residue content of a composite sample of apples of a total of *K* elements, υi is the random individual variability that is characteristic of the given apple (individual chemical residue / average chemical residue content), *m* is the individual mass of the given apple. The process was repeated with every single day of consumption. The typical values of the resulting distribution are presented in Table 2.

Table 2

Typical percentiles of captan intake from apple consumption

Percentile →	95	98	99	99.99
General population (µg/kgbw/day)	4.8	10	16	133
women aged 15–45 (µg/kgbw/day)	4.01	8.1	12	53.8

Source: Zentai et al., 2013

Captan's acute reference dose is 300 µg/kgbw (JMPR, 2004), established for childbearing age women. Even the high percentiles of the resulting distribution were well below the reference value. Accordingly, in the case of the calculated exposures no health risk needs to be expected.

Estimating the combined (cumulative) intake of pesticides of similar effects

Estimating the combined intakes of food contaminants of similar toxicological effects is a major challenge to food safety risk assessment today. The so-called cumulative risk assessment is a priority subject in regard to both human and environmental risk assessment, for which the elaboration and harmonization of procedures is on the agenda of the relevant regulatory bodies.

A consumer will consume multiple food products each day, which may contain multiple different chemical residues of similar mechanisms of action. Their intakes need to be assessed together, since their effects accumulate. The toxicological effects of two or more substances may appear in three different forms: *independent action*, similar action (dose aggregation) and interaction.

The RPF (relative potency factor) approach based on aggregating the doses concerned is considered to be a suitable method for assessing the cumulative dietary intake of compounds of similar mechanisms of action (Jensen et al., 2013; Kennedy et al., 2015). Doses are aggregated when the compounds concerned have similar mechanisms of action but different levels of toxicity. In such cases the combined effect of the compounds present can be established by aggregating the quantities of the compounds, adjusted for potency.

The relative potency factor method relies on the identification of an index compound, with the reference point of which (NOAEL or BMD) are the reference points of the other compounds compared (RPF), and the combined toxicity of the compounds is expressed in index compound equivalent by multiplying the various concentrations with the relevant relative potency factors and then aggregating the results. The combined (aggregate) exposure is compared with the reference value (ADI or ARfD) of the index compound.

I studied the intake of organophosphorous pesticide residues stemming from the consumption of foodstuffs made from plants (vegetables, fruits). Of the residue measurements pertaining to the selected product I focused on organophosphorous compounds. Based on the RPF approach I chose acephate as index compound and for every single sample I calculated the aggregated concentration of organophosphorous residues expressed in terms of acephate equivalent, using the RPF factors found in relevant publications (Caldas et al., 2006; Boon et al., 2008).

Thereafter I multiplied the masses of the products consumed on the given day by the relevant acephate equivalent concentrations, and I aggregated the intakes of the various products so calculated, in each combination, for the given day of consumption. To demonstrate with a simple example: if a consumer had green peppers, tomatoes and cucumbers on a given day for which 3, 6 and 4 aggregated acephate residue concentrations were available, the estimated exposure is as follows. For green peppers and tomatoes 3 and 6 possible intake values are calculated, respectively. Adding these results in 3 × 6 = 18 possible combinations. For cucumber a total of 4 intake values are possible: adding these to each green pepper and tomato intake aggregates produces a total of 18 × 4 = 72 possible combinations. Carrying out the process with the daily consumptions of each consumer, the resulting distribution's relevant percentile characterizes the cumulative intake (Table 3).

Table 3

Typical percentile values of the cumulative intake of organophosphorous residues*

Total population (%)	**Percentile values of daily exposure (µg/kgbw/day)**				
	P 0.975	**P 0.99**	**P 0.995**	**P 0.999**	**P 0.9999**
Max	184.6	188.1	194.8	214.9	215.2
99.999	178.2	182	189.3	207.7	209.5
99.99	135.7	139.1	146.8	150.2	157.5
99.95	86.9	87.3	87.6	91.5	97
99	24.6	25.3	26.4	27.7	30.3
97.5	15.8	16.8	17.6	18.6	20
Median	0.9	1.2	1.4	1.7	2.2

Note: *The daily exposure columns contain data of the typical percentiles of the distribution of the intake combinations calculated for the various days of consumption (i.e. the variability of the possible intakes of the given days of consumption). The data in the column for the entire population indicate the typical percentile values selected from the distribution of these percentile values (the variability of the population's intake).

Source: Zentai et al., 2016

Acephate's acute reference dose is 100 µg/kgbw (JMPR, 2005). In regard to the distribution of the 99th percentile intake data calculated for the various days of consumption the cumulative intake remains below the reference level on 99.95% of the days of consumption. It should be noted that the application of the relative potency factor method requires a very careful approach. The European Food Safety Authority (EFSA, 2012) emphasized in relation to its definition that toxicological information should preferably originate from an assessment of the same species under similar circumstances. Where different uncertainty factors are applied, those should be adjusted before the RPF calculation. Moreover, the index compound should have a good toxicological description of the combined effect. In this regard exposure estimation is, to some extent, interlinked with toxicological considerations. For this reason, in my calculations I used relative potency factors already published by other authors.

Conclusion

Due to the need for using large quantities of data, working out risk estimates requires software support. One such program, which is applied in Europe, is called MCRA *(Monte Carlo Risk Assessment)*, whose development is based on the most recent recommendations. The development of this particular software tool is a continuous effort in view of suggestions and proposals received from users and other stakeholders. Should it get to be widely adopted as a routinely applied technique in other countries, its introduction in Hungary may also be worth considering.

The paper highlights the complexity of dietary risk (exposure) assessment, reflecting that regulatory institutions are making efforts at developing a harmonised methodology. The use of probabilistic techniques will become indispensable in risk assessment in the future; given the amount and type of information required these methods necessitate carefully planned and well organized data collection and storage as well. Growing consumer awareness, the introduction of new active ingredients and the development of analytical techniques call for up-to-date methods of assessment and estimation and require the availability of authentic information on the (combined) effects of harmful substances entering the human body.

With the help of the methods that have been developed we have proven that probabilistic techniques can be adapted to risk assessment considering domestic databases even without any specific major software background. The methods worked out enable – if sufficient quantities of data are available – the characterization of the intake through food consumption of any food contaminant, additive or plant protection product residue and the drawing of conclusions concerning risks facing the Hungarian population.

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