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A semi-quantitative model for risk appreciation and risk weighing

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ABSTRACT

Risk managers need detailed information on (1) the type of effect, (2) the size (severity) of the expected effect(s) and (3) the fraction of the population at risk to decide on well-balanced risk reduction measures. A previously developed integrated probabilistic risk assessment (IPRA) model provides quantitative information on these three parameters. A semi-quantitative tool is presented that combines information on these parameters into easy-readable charts that will facilitate risk evaluations of exposure situations and decisions on risk reduction measures. This tool is based on a concept of health impact categorization that has been successfully in force for several years within several emergency planning programs. Four health impact categories are distinguished: No-Health Impact, Low-Health Impact, Moderate-Health Impact and Severe-Health Impact. Two different charts are presented to graphically present the information on the three parameters of interest. A bar plot provides an overview of all health effects involved, including information on the fraction of the exposed population in each of the four health impact categories. Secondly, a Health Impact Chart is presented to provide more detailed information on the estimated health impact in a given exposure situation. These graphs will facilitate the discussions on appropriate risk reduction measures to be taken.

1. Introduction

The interest in and the need for tools that can provide quantitative risk assessments has increased in recent years. Risk managers are challenged to decide on appropriate risk reduction measures that are well-balanced in terms of health-effectiveness as well as cost-effectiveness. For instance, in situations where consumption of a food or food substance may induce both a health risk and a health benefit, a risk manager needs tools to weigh these risks and benefits in a quantitative way. The sixth Scientific Colloquium organized by the European Food Safety Authority (EFSA) in July 2006 aimed to have an open scientific debate on the methods and approaches for risk–benefit analysis of foods (EFSA, 2007). It was stated that "the risk–benefit analysis should contain a means, quantitative if possible, to compare/weigh the potential risk against the potential benefit". The process of risk–benefit analyses was further mentioned to involve "the weighing of the likelihood and severity of a hazard against the likelihood and magnitude of a benefit". Risk–benefit analyses may also include weighing the benefit of a reduced risk of adverse health effects by, e.g. mycotoxins through the application of fungicides and the potential risks associated with residues of these fungicides.

Secondly, in situations where multiple risks are present a risk manager may have to identify the risk that should be given the highest priority or how and in which situation (limited) resources can be best deployed such that the greatest benefits can be achieved in terms of reduction of health risks. For instance, one chemical may cause concern because of a large fraction of the population being at risk, while another chemical causes a more severe type of effect in a relatively small fraction of the population.

Until now, risk assessments are mostly carried out using a deterministic (and often conservative) approach rather than a

Abbreviations: AChE, acetyl cholinesterase; ADI, Acceptable Daily Intake; AEGL, Acute Exposure Guideline Level; CED, critical effect dose; CES, critical effect size; DALY, disability adjusted life years; DON, deoxynivalenol; ERP, emergency response planning; ERPG, Emergency Response Planning Guidelines; HBGV, Health-Based Guidance Value; HIC, health impact criterion; ICED, individual critical effect dose; IEXP, individual exposure; IMoE, individual margin of exposure; IPRA, integrated probabilistic risk assessment; LHI, Low-Health Impact; LOAEL, lowest-observed-adverse-effect level; MHI, Moderate-Health Impact; MoE, margin of exposure; NHI, No-Health Impact; NOAEL, no-observed-adverse-effect level; PHIA, probabilistic health impact assessment; PoCE, probability of critical exposure; SHI, Severe-Health Impact; TDI, Tolerable Daily Intake.

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more quantitative, probabilistic approach. One of the approaches used is the comparison of (food-borne) exposures with a Health-Based Guidance Value (HBGV) such as the acceptable (or tolerable) daily intake (ADI or TDI). In this approach, no appreciable health risk is expected if the estimated exposure is below the HBGV, or a health risk cannot be excluded if the HBGV is exceeded. An alternative approach of safety assessment is the evaluation of the margin of exposure (MoE), i.e. the ratio of the no-observed-adverse-effect level (NOAEL) and an exposure estimate. These traditional deterministic risk assessment approaches are predominantly aimed at protection, i.e. determining situations of no-risk, and use conservative assumptions. As a consequence, even when a health risk is estimated, these approaches do not provide quantitative information on the actual risk. For instance, if the MoE is similar for two separate chemicals this does not imply that the associated risks are similar. This will depend on many factors like the type of effect (e.g. slight irritation versus teratogenicity), the steepness of the dose–response curves, the fraction of the population at risk, etc.

Probabilistic tools are promising to estimate quantitative health risks from exposure to chemicals. Van der Voet and Slob (2007) presented the basics for a new tool: the integrated probabilistic risk assessment (IPRA) model. This model integrates a probabilistic hazard characterization with a probabilistic exposure assessment. The IPRA-model aims at a quantitative risk assessment by taking both variability among humans and uncertainty in data and assumptions into account. The present paper uses this model to develop a tool that provides the risk manager with all the necessary information in a transparent form such that appropriate choices for risk reduction measures can be taken. Moreover, the tool will allow estimation of the consequences of risk reduction measures beforehand. This will facilitate weighing the costs and the benefits in health impact of risk reduction measures.

2. Basic concept

For an adequate interpretation of the health impact of a given exposure situation a risk manager needs information on at least three parameters: (1), the type of effect(s) expected to occur, (2) the size (i.e. degree of severity or seriousness) of these expected effect(s) and (3) the fraction of the population at risk in the given exposure situation. Preferably, this information should be provided to the risk manager in a transparent and easy-to-read way. Then the question arises how to combine these three parameters expressed on different scales into one single dimension.

2.1. The type of effect(s)

The urgency for risk reduction measures will depend on the type of effect. For instance, the occurrence of some local irritation might be considered as inducing a smaller health impact (and thus as a less urgent problem) than the occurrence of teratogenic effects. Generally, human risk assessment has to rely on data obtained from animal experiments. It is then assumed that the toxicity profile observed in animals has a predictive value for the human toxicity profile. (It is noted that for genotoxic carcinogens the predictive value of animal experiments is more towards potency rather than tumour type. Although the present paper focuses on non-tumourigenic endpoints the basic concept can be extended to (genotoxic) carcinogens). Regulatory standards or HBGVs are based on the most critical effect but it should be taken into account that once an HBGV is significantly exceeded other effects may also become apparent. The occurrence of additional effects should be considered in the risk assessment process as will be illustrated by the example of the mycotoxin deoxynivalenol.

2.2. Effect size

The crucial step for a quantitative Health Impact Assessment is to translate effect sizes on possibly very different scales to a common basis. The traditional deterministic risk assessment based on the determination of a NOAEL does not provide the information on the degree of adversity and does not allow the combination of values obtained from different studies or substances to a same scale. A NOAEL will be the highest dose at which the observed effect size does not statistically significantly differ from that in the control group. Hence, a NOAEL is, among others, determined by the choice of dose-spacing and the number of animals per dose group and, as opposed to a Benchmark dose, is not associated with a predetermined change or response in a toxicological parameter. It should be noted that in some situations the effect size observed at the NOAEL or the LOAEL (lowest-observed-adverse-effect level) and its biological relevance are considered in the interpretation of the final outcome of the risk assessment process. However this occurs on a case-by-case basis and clear guidance is absent. Besides, the observed effect size is only an estimate, the imprecision of which is typically ignored. A NOAEL is therefore not a suitable point of departure in a quantitative risk assessment and dose–response modelling deserves preference. Slob and Pieters (1998) have introduced the term critical effect size (CES) for dose–response modelling of continuous endpoints. Dose–response modelling provides quantitative information on the relation between a particular exposure and the estimated effect size at that exposure. The CES is expressed as a percent change in the group mean as compared to the control group mean (e.g. 20% reduction in acetylcholine-esterase activity). It reflects the quantitative change in a particular endpoint considered as nonadverse at the level of an individual. But of course, a CES can be specified at any nominal level. For instance, a CES of 5% may be used to demarcate minimal effects, and 10% for mild effects (for a given endpoint). The dose associated with a particular CES is called the critical effect dose (CED).

For an adequate interpretation of the outcome of a quantitative risk assessment, risk managers need guidance on how to judge the effects expected in the exposed population in terms of severity or seriousness. This means that not only a CES should be defined but also clear judgements in terms of health impact of effects sizes above the CES are unavoidable.

2.3. Fraction of the population at risk

The fraction of the population at risk can be estimated by use of the IPRA-model (Van der Voet and Slob, 2007; Van der Voet et al., 2009). In brief, this model integrates a distribution of individual critical effect doses (ICED), being the dose associated with a person's individual critical effect size (CES) (see above under "Effect size"), with a distribution of Individual Exposures (IEXP). The ratio of these distributions (ICED/IEXP) is calculated by Monte Carlo analysis and results in a distribution of Individual Margins of Exposure (IMoE). The final outcome of this assessment is either a low percentile (e.g. P_1 or $P_{0.1}$) of this distribution or the probability of critical exposure (PoCE), i.e. the probability 'that IMoE is below 1'. This PoCE can be interpreted as the fraction of the exposed population at risk. It should be noted that this fraction consists of individuals who are either more susceptible, or who have a relatively high exposure to a chemical or a combination of both.

2.4. Possibilities for combining the parameters of interest

As a first thought, combining the three parameters (type of effect(s), effect size, fraction of the population at risk) into one overall parameter on a continuous scale may be the most preferable option. The present risk assessment procedures (i.e. safety