3. Quantitative Risk Assessment of Combined Exposure to Food Contaminants and Natural Toxins

Objectives:
- To perform probabilistic risk modelling (exposure as well as effects) of food contaminants and natural toxins.
- To perform Pan-European risk modelling using different national food consumption databases simultaneously, including exposure of vulnerable groups.
- To evaluate uncertainties in risk assessment, *i.e.* exposure, occurrence of adverse effects, and variations in susceptibility.
- To perform uncertainty analyses for different chemicals to demonstrate the impact of uncertainty in data, risk models, and assumptions made on variables in the assessment.
- To develop criteria for comparative risk analysis.
- To develop probabilistic models to evaluate the risk of combined exposure of chemical contaminants and natural toxins including validation of the statistics and taking into account, where appropriate, nutrition and labelling aspects.
- To contribute to building a new integrated risk analysis approach for foods which is based on qualitative and quantitative data.
- To actively make use of completed and currently on-going research based on these specified in the earlier sections of this technical annex.

Compounds: pesticides, mycotoxins, environmental contaminants and natural toxicants

Co-ordinator: Partner 17, NFA

Partners	**Contribution**
1 RIKILT (Inst. Food Safety; NL)	exposure models and integration Dutch data
14 RIVM (Nat. Inst. Pub. Health Env.; NL)	modelling hazard characterisation and comparing toxic effects
16 BAG (Fed. Off. Pub. Health; CH)	natural toxins, dose response data, Swiss data
17 NFA (Nat. Food Admin.; SE)	criteria for combined exposure, Swedish data
6 ISS (Inst. Pub. Health, I)	residue data exchange, Italian data
18 NINFS (Nat. Inst Food Saf. Nutr.; CHN)	comparing risk China vs Europe, Chinese data
19 DFVF (Inst. Food Saf. Toxicol., DK)	cumulative risk and Danish data
20 NIPH (Nat. Inst. Pub. Health, CZ)	model testing and Czech data
33 IRAS (Inst. For Risk Ass. Sci, NL)	modelling hazard characterisation and comparing toxic effects

Deliverables:
- Paper on concentration data quality and availability of different agricultural production systems.
- Extended Monte Carlo Risk Analysis-software and an user-friendly, interoperable EU harmonised food consumption database approach for modelling exposure. Performance of probabilistic exposure assessments of contaminants and natural toxins including validation of the statistics and taking into account, where appropriate, nutrition and labelling aspects.
- Algorithms (statistical rules) for effect modelling including dose-response modelling and bench mark approach.
- Paper regarding availability of toxicity data relevant for bench mark dose modelling.
- Position paper on qualitative and quantitative criteria and methodology of comparative hazard identification.
- Paper on differences in residue monitoring and risk assessment procedures between China and Europe.
- Quantitative risk model combining data from hazard characterisation and exposure assessment, including statistical possibility of uncertainty analyses of all steps in the risk assessment procedure.
- Paper(s) on qualitative and quantitative results of combined exposure to various chemicals in the food chain, including an overview of the qualitative and quantitative uncertainties of the assessment.

The development of databases and improved access to data on contamination and food composition from the various production systems will be an essential part of this IP. Qualitative and quantitative criteria will be developed for comparative risk assessment of mixtures of chemicals, qualitative and quantitative uncertainties in the assessment will be analysed, and input will be given in the new integrated risk analysis model.

The primary aspects to be addressed in the workpackage are:

1. How to integrate exposure and effect modelling into quantitative risk modelling.
2. How to set qualitative and quantitative criteria for comparing effects of various food chemicals and natural toxins to be used in combined exposure to food chemicals.
3. How to address qualitative and quantitative uncertainty and variability in various parts of the quantitative risk assessment.
4. How to make better use of available consumption databases in combined exposure to food chemicals to describe exposure of different European populations including vulnerable groups.

This workpackage will contribute in building a new integrated risk analysis approach for foods.

Workplan

Starting point
The project will start with a comparison of the occurrence of relevant pesticides, mycotoxins and natural toxins in foods produced by different agricultural practices. For these chemicals a single compound probabilistic exposure assessment will be performed in the first 18 months.
From work performed until month 18, but also from workpackage 1 or 2, other chemicals may appear to be relevant in the comparison. Month 18 will therefore be an important mile stone. Building upon all elements/projects/deliverables of the first 18 months a concept of a quantitative risk assessment model will be discussed during a workshop and decisions will be made on further exploration and extension of the quantitative risk assessment model.

In the first two months of the project partners will make a protocol to indicate how the different tasks will be tackled. In month 3, protocols will be discussed and an extensive training will be held to harmonise data collection and data use in models. All partners will be trained regarding effect and exposure modelling needed to perform the tasks within this workpackage. Discussing protocols and training will be an important milestone in order to guarantee a harmonised and well-balanced approach of all tasks needed.

Estimated month 12 will also be an important moment/milestone to check plans, protocols and expectations with reality.

3.1 Residue data on pesticides, mycotoxins and natural toxins in foods from different production practices

Residue data on pesticides, mycotoxins and natural toxins in different food products as well as the amounts of foods consumed are relevant when determining dietary exposure. For residue data it is important to consider variability within measurements and uncertainty (limited data sets). Despite uncertainty analyses a minimum of data is needed. Residue data from foods of high input systems will be derived from residue monitoring programmes, from SCOOP-projects or from data generated in national survey programmes and further input form other either completed and or on-going EC-supported research projects will also be sought. Most partners will ensure access to these type of data at a national or international level. Data on natural toxins will be derived from the BASIS-database (product of previous EU projects BASIS and the NETTOX-Concerted Action).

Partner RIKILT will develop a Microsoft Access database to harmonise the compilation of residue data generated within the institutes of all partners. Partner RIKILT will train the other partners to use this database in order to guarantee compatibility between partners and with the Monte Carlo

Risk Assessment (MCRA)-software. Based on the information on number of samples and quality of all data points, the variability within each data set will be described.

Partner ISS and RIVM/ IRAS will ensure access to the SCOOP data on natural toxins . Specific data on foods from low input agricultural production systems will be collected, and the literature will be searched for other relevant data. All partners will search for surveys generating data regarding low input chemical production systems within their own countries. Relevant data will be downloaded into a Microsoft Access database.

Partners RIVM, BAG and NFA have been actively involved in filling the BASIS database containing residue and toxicological data of natural toxins. Relevant data of different natural toxins (possible elevated levels, small margin between exposure levels and toxicity, type of toxic effects, etc.) will be selected from the BASIS database and from up-to-date literature. Partner BAG will compile this information in a useful format and will upload the data via Internet to the Monte Carlo – MCRA software using the summary statistic data option of this software.

Partner ISS will compose a position paper on availability, quality and access of data on pesticide residues, mycotoxins and natural toxins in foods from different production practices and breeding methods, relevant for the comparative risk assessment. Partner ISS provides data on mycotoxins. Partner BAG will support this activity by providing data of natural toxins and partner RIKILT will provide data of pesticides.

The Institute of Nutrition and Food Safety, Beijing, China (NINFS) is the WHO collaborating centre for residue monitoring in food in China. The NINFS has established the national monitoring for chemical contamination, mainly focused on the GEMS/Food core list, e.g. pestcides and mycotoxins. Partner NINFS will describe the monitoring systems within China, also in relation to data collection and the availability of analytical methods to perform food safety monitoring for different chemicals. Partner NINFS will organise the food consumption data to be used in exposure modeling. This partner will also describe risk assessment procedures for mycotoxins and pesticides in China. Partners RIKILT and RIVM/ IRAS will compare these with the European risk assessment procedures.

Training

Probabilistic models have been released recently, but the technique is data dependent, the models are much more complicated than existing risk assessment procedures, and modelling is a new technique in risk assessment. Partners RIKILT and RIVM have developed probabilistic models, but other partners have to be trained to learn all details of these new probabilistic models. Partner RIKILT will be responsible for a training on exposure models (www2.rikilt.dlo.nl/mcra/mcra.html) and partner RIVM/ IRAS will be responsible for training the principles of effect modelling.
The models are data dependent and the compatibility between data on residue levels, food consumption and toxicity is of utmost importance. The training will also focus on the use of standardised Microsoft Access databases for compatibility between partners in data collection and with the Internet software. The training will also indicate rules regarding uncertainty analyses.

In addition to the training an exchange between China (partner NINHS), Italy (partner ISS), the Czech Republic (partner NIPH) and The Netherlands (partners RIKILT and RIVM/ IRAS) will be established in order to look for further co-operation and harmonisation in relevant area’s of risk assessment in general and risk modelling in particular.

The budget has allowed in the range of 15 exchanges for training activities associated with the project. This number is based on a average stay of one week per person applying the general EC rule for travels expenses and no distinction between the various labour categories (i.e. senior scientist, Ph D students, technicians)

After 18 months training is foreseen for others than the partners in this workpackage

3.2 Modelling exposure and harmonising food consumption databases

Food consumption databases processed by RIKILT, NFA, DFVF ISS and subcontractor INRAN will be used in the exposure assessment for single chemicals in the first part of the project (until month 18). After 18 months food consumption data form China (NINFS) and Czech Republic (NIPH) will be incorporated as well.

In the first 18 months the food consumption databases will be used to test the model. After 18 months the food consumption data (coding) will be harmonised in a suitable format to be compatible with the probabilistic software and the consumption data will be used simultaneously in more advanced risk modelling (see also 3.4 and 3.5).

Partners RIKILT, NFA, ISS and DFVF will therefore organise their food consumption in a MS-Access database compatible with the MCRA-software (before 18 months). Partners NINFS and NIPH will do so after 18 months. The data will be organised in a similar way and will be made accessible for all partners to be used in risk assessment procedures.
Partners RIKILT, NFA and DFVF will also harmonise their pesticide data from their national monitoring programmes and will perform probabilistic exposure assessments for single pesticides before month 18.

The MCRA-software statistical subroutines will be developed for long-term intake of rarely found contaminants to which only a small percentage of the population might be exposed. Partners RIKILT and RIVM/ IRAS will optimise MCRA-software by adding relevant statistical subroutines of long-term exposure for rarely found chemicals into the software.

Partner BAG will perform probabilistic exposure assessments using natural toxin data of many different compounds with the MCRA-software. Within the MCRA-software there is an option to use summary data (only average, maximum, number of samples are stated), a format in which most of the natural toxins are reported. Partners RIKILT and BAG will characterise the uncertainty and variability in these data sets in relation to variability in exposure.

Partner ISS will perform probabilistic exposure assessments to describe the uncertainty and variability in mycotoxin data using summary data and full data sets for different mycotoxins.

3.3 Uncertainty analysis, effect modelling and comparative risk assessment

Partner RIKILT will use statistical techniques, like bootstrapping, to estimate the uncertainty in exposure data and partner RIVM/ IRAS will use similar techniques to address the uncertainty in toxicity data. All partners involved in the exposure assessment (see project 2) will perform their assessments, including a sensitivity analysis (e.g. effect on the exposure of assumptions regarding possible concentration levels below the limit of detection).

The so-called bench mark dose (BMD), i.e. the ‘ statistical lower confidence limit for a dose that produces a predetermined change in response rate of an adverse effect compared to background’, will be further developed. Consequently, a special developed software such as ToxRisk software by US-EPA or PROAST by RIVM (The Netherlands), will be explored further by partner RIVM/ IRAS. The applicability of the bench mark dose approach by comparing it with the “classical” NOAEL approach, using data of different chemicals also be further examined by partner RIVM/ IRAS. Partner BAG will search in international databases and will compose a position paper on available toxicological data (dose response information) for several pesticides, mycotoxins and natural toxins. Partners RIKILT and NFA will deliver input of their national toxicity database systems.

As *comparative* risk assessment may vary significantly, because design and conduct of toxicological studies may influence the shape of the dose-response curve, the following techniques will be checked for applicability in order to compare health risks:

a) Disability-Adjusted Life Years and Life Cycle Assessment
Existing LCA (Life Cycle Assessment) approaches can be classified into two categories: 1) potency-based (reflecting the probability of risk or effect, and 2) severity-based (sometimes termed "damage" and reflecting the consequences of potential effect in addition to likelihood). Partners RIVM/ IRAS and NFA will reflect on the applicability of Life Cycle Assessment and DALY concepts for contaminants, natural toxins, mycotoxins and pesticides.

b) Classification systems
Another possibility which will be pursued is the relatively simple classification system as proposed by the International Life Sciences Institute (ILSI) to classify chemicals into three categories, 1) irreversible, life-shortening, 2) may be reversible, could be life shortening, and 3) generally reversible, not life shortening. Partner NFA will explore these systems and will prepare a position paper on the usefulness of these systems. Partners RIVM/ IRAS and BAG will be helpful with input of information available at their institutes.

3.4 Integration of toxicity models and exposure models, building risk models

After month 18 the toxicity and exposure models will be integrated by partners RIKILT and RIVM/ IRAS. This includes the toxic endpoints generated in the project of uncertainty analysis, effect modelling and comparative risk assessment by partner BAG and a classification of chemicals created by partner NFA. Margins of exposure (MoE), including an indication of uncertainty, will be calculated for various chemicals. Next to the MoE the severity of the toxic effect will be considered and classified. A workshop will be held to discuss this approach with risk managers. In such a workshop also relevant endpoints when comparing results of probabilistic approaches with those of deterministic approaches will be addressed.

3.5 Extending the models with new data

Building upon the results of the project modelling exposure and harmonisation of food consumption databases, the harmonised approach of using food consumption data in exposure assessment will be extended with Chinese consumption (partner NINFS) data and data from Czech Republic (partner NIPH). Compatibility issues between consumption data and residue data will be considered. The project results will also be disseminated to international organisations like EU Standing Committee's and the CCPR. The toxicity models such as the bench mark approach and other models (e.g. not-threshold chemicals) will be build into the quantitative risk model.
As a result of the work done in WP1 and WP2 during the first 18 months other critical chemicals than mycotoxins, natural toxins or pesticides might appear to be relevant in combined exposure or when comparing high- and low-input production systems. All partners will search for concentration data in regular monitoring programs. A search for toxicity data of these chemicals will also be performed.

3.6 Applying the models in quantitative risk assessment of combined exposure

For chemicals with the same mode of action cumulative risk models will be used. Uncertainties will be addressed regarding the duration of the exposure in relation to the duration of effects.

Not only man-made chemicals like pesticide have the above-mentioned toxic effects. Also a number of natural toxins may cause similar effects. Various combinations of chemicals and natural toxins will be tested based on the bench mark dose approach (and other approaches developed in this project), comparable toxic endpoints and severity of toxic effects. Comparison will also be made regarding the occurrence of natural toxins in different production systems.