Report of IPRA workshop 2012

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Abstract

On the 12th and 13th of December 2012 the Dutch Food and Consumer Product Safety Authority (NVWA) and the RIVM organized an international workshop on Integrated Probabilistic Risk Assessment (IPRA). With IPRA the risk of exposure to a substance in food is assessed in a probabilistic manner (both exposure and hazard). The tool combines two existing methods: 1) probabilistic exposure assessment and 2) the bench mark dose approach and is ready to be used. The goals of the workshop were to share knowledge and to analyse possibilities of IPRA as a methodology to assess risks of substances in food. The participants were informed on the concepts of IPRA and discussed the use, practicability and place of IPRA in risk assessment. The general opinion of the participants on the use of IPRA was that IPRA is sufficiently developed to be shared with other risk assessors, on an international level. In addition, the participants were of the opinion that risk managers can be inspired to use IPRA as a tool for refined, higher tier risk assessments.

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Summary

On the 12th and 13th of December 2012 an international workshop on Integrated Probabilistic Risk Assessment (IPRA) was held at the premises of the Dutch Food and Consumer Product Safety Authority (NVWA) in Utrecht. The goals of the workshop were to share knowledge and to analyse possibilities of IPRA in dealing with risks of substances in food. The 22 participants of the workshop were informed about the concept of IPRA (Day 1) and discussed the use, practicability and place of IPRA in risk assessment (Day 2).

Probabilistic analyses are undertaken because uncertainties are inherent in risk assessment and, just as variability, need to be taken into account. Probabilistic risk assessment may be used in higher tier assessments, while deterministic methods may be used at lower tiers. Whereas in earlier days only the exposure part of the risk assessment was performed in a probabilistic manner, presently also the 'hazard-side' of the assessment is often carried out with a probabilistic approach. IPRA integrates the two approaches into one.

Exposure to substances in food is generally assessed by combining concentration data in food with types and amounts of food consumed (per kg bodyweight). The output of an exposure assessment is an (acute or chronic) exposure distribution for the population, including the uncertainty in the exposure. At the 'hazard-side' of IPRA, dose-response data are evaluated; all curves that fit the data are accepted. For each of the curves the bench mark dose (BMD) is calculated, in order to obtain an uncertainty distribution for this parameter. Subsequently, the BMD-distribution is extrapolated to the (sensitive) human, by using intra- and interspecies extrapolation factors distributions. IPRA combines the resulting distribution with the exposure distribution, yielding the key output of IPRA: the severity of the effect, the fraction of the population with that degree of effect and the uncertainty of this fraction. In addition, the contribution of the different sources to the total uncertainty is provided as output. The workshop participants concluded that the presented bar plots are a good way to visualize the output of IPRA. The choice for showing a certain percentile (e.g. the 1st, which is the present default) was considered a subject for discussion between risk assessors and risk managers.

The general opinion of the participants on the use of IPRA was that the tool is sufficiently developed to bring it further to other risk assessors, on an international level. In addition, the participants believed that risk managers can be stimulated to use IPRA as a tool for refined, higher tier risk assessments. It should be noted that IPRA is not a completely new method, and the tools are ready to be used. In addition, it may be useful to have software that enables risk managers to choose in what manner to present the results. It was recommended that the small network, arisen from this workshop, should engage their colleagues; and to try to enthusiast people at national, and in parallel at European, level.

1 Introduction

On the 12th and 13th of December 2012 a workshop on Integrated Probabilistic Risk Assessment (IPRA) was held at the premises of the Dutch Food and Consumer Product Safety Authority (NVWA) in Utrecht. Twenty two participants from 8 different EU member states, were informed about the concept of IPRA (Day 1) and discussed about its use, practicability and place in risk assessment (Day 2). The programme and the list of participants can be found in Appendix 1 and 2, respectively.

In his welcome speech Hubert Noteborn, head of the Unit of Integrated Risk Assessment of the Office for Risk Assessment and Research of the NVWA mentioned the goals of the workshop, which are to share knowledge and to analyse possibilities of IPRA in dealing with risks of substances in our food. Hubert Noteborn explained that in national risk assessment there is a call for transparency, which means performing a risk assessment under real-life conditions focusing on the high-risk subgroups upon exposure to substances in food. Second, a clear communication about the certainties and the uncertainties in the assessments is needed. The Office thinks that time has come to discuss the application of the integrated probabilistic risk assessment approach. In the current system of risk assessment, when exposure exceeds the health-based limit value, it is unclear how severe the effects might be and what fraction of the population might be affected. The usual conclusion in such situations is that health effects in the human population cannot be excluded. A frustrating situation, for the risk assessor, the risk manager and the consumer.

The traditional NOAEL approach is usually based on a worst case, performing a conservative assessment using point values. This deterministic approach does not discriminate between variability and uncertainty and makes in Hubert Noteborn's view too conservative estimates for health-based limit values. The Office thinks that it is fair to put forward that the NOAEL approach is inconclusive in the everyday life of a risk assessor and risk manager at a food safety authority. On the one hand, there is a great need to quantify the percentage of the population affected, and on the other hand, to quantify uncertainty. Furthermore, there is the need of a close interaction between toxicologists, exposure experts, risk assessors, and risk managers. Because they need to agree upon the definition of the target subpopulation, and the way outcomes should be reported to risk managers. Hubert Noteborn considers a deterministic approach suitable as a first tier approach to risk assessment: it may indicate that even in a worst-case scenario no notable risk is expected. However, if the worst-case assessment indicates that risks cannot be excluded, a more realistic assessment may be required to get better and more quantified information on how large the risk might be and who is affected.

Hubert Noteborn invited the participants to assess IPRA on its merits and to elaborate on how we collectively could shape the application of IPRA in our daily work as risk assessors.

2 Day 1: the concept of IPRA

2.1 Jacob van Klaveren: From dietary probabilistic modelling towards IPRA

Jacob van Klaveren explained that while probabilistic risk assessment is available, deterministic assessments are, and will still be used, as a lower tier approach. Probabilistic risk assessment may be used in higher tier assessments, which is also put to paper in the EFSA strategy. Examples are available that EFSA starts to implement probabilistic assessment in their daily work. Jacob van Klaveren mentioned that the conceptual thinking on integrated probabilistic risk assessment already started in the period 2004-2008 in the FP7 project SAFEFOODS. In this project software has been developed and used by several partners. The SAFEFOODS project was followed by work at Biometris (Wageningen University) and RIVM/RIKILT to apply the software for the issues that will be discussed in the current workshop. This work was kindly sponsored by the NVWA.

Whereas in the earlier days only the exposure part of the risk assessment was done in a probabilistic way (for example with the Monte Carlo Risk Assessment platform), presently also the 'hazard-side' of the assessment is often carried out with a probabilistic approach (BMD). IPRA integrates the two approaches into one.
Jacob van Klaveren argued that risk assessment covers more than science alone: stakeholders involvement is important. He gave the example of pesticides, where stakeholders are NGOs, farmers associations, and the pesticide industry. He explained the work in the ETUI-project (sponsored by EFSA), which explored the best way to calculate the usual (=long-term) intake, based on food consumption surveys with a short duration. This was consequently implemented in MCRA. He also mentioned the work on probabilistic exposure assessment in the FP7 project ACROPOLIS, in which MCRA is used to estimate the cumulative (sum of substances with the same mode of action) and aggregate (sum of all routes) exposure to specific pesticides.

The questions to Jacob van Klaveren were about the ETUI-project: Rob Theelen asked which of the distributions shown is the best model. The answer was that the modelled usual intake is the best estimate of the long-term intake; the other two distributions are the single day intake distribution and the observed mean intake of the two days for the individuals. Bernard Bottex inquired if there has been a validation of this model for usual intake. Yes, simulation studies were used for validation, and in addition a comparison with duplicate diet studies and biomarkers was made in several projects.

2.2 Hilko van der Voet: Probabilistic modelling and exposure assessment using MCRA 7.1

IPRA is conceptually an elaboration of probabilistic exposure assessment, and technically the currently available IPRA software is an extension of the web-based platform for Monte Carlo Risk Assessment (MCRA Release 7.1,

mcra.rivm.nl). MCRA and IPRA share the same principles regarding modelling of variability and uncertainty.

Hilko van der Voet explained that in deterministic exposure assessment many conservative estimates are combined into one estimate, which is then overly conservative. In probabilistic exposure assessment distributions are used for many parameters: e.g. food consumption amounts, body weights, concentrations of compounds in a food sample. These are combined in the assessment, using Monte Carlo sampling, resulting in a more realistic exposure estimate.

Basic inputs for an exposure assessment with MCRA are the following: concentration data, types and amounts of food consumed and individual body weights. Additional inputs may be e.g. food conversion factors, unit weights, processing factors. In MCRA models for acute and chronic exposure are implemented. Chronic exposure can be estimated using either a simple –naïve- method or parametric models such as those that resulted from the ETUI-project. Hilko van der Voet explained the difference between variability, which is the variation (e.g. between individuals) existing in the real world and uncertainty, which is the lack of knowledge. The latter can be reduced when knowledge increases. In MCRA the variability and uncertainty are calculated using an inner and outer 'loop'. In the inner loop the intake variability between person days is calculated, creating one intake distribution curve from the offered data set, while in the outer loop the uncertainty is calculated, using resampled data sets with the bootstrap method, creating many distribution curves. A full integration of IPRA and MCRA in version 8.0 is expected in 2013.

Gerhard Heinemeyer asked how the qualitative uncertainty of an assessment is dealt with. He mentioned the IPCS guidelines, which say that you should get an idea of uncertainty by doing sensitivity analyses. Hilko van der Voet replied that presently this is done according to EFSA Guidance (the tabular format), which is also available as an add-on to MCRA. He added that when it is known how to quantify a specific uncertainty, this calculation could be added to MCRA.

2.3 Wout Slob: Principles of IPRA

Probabilistic analysis: general information
Wout Slob explained that we use probabilistic analysis because uncertainties are inherent in risk assessment, and we also want to take into account variability. We try to capture both variability and uncertainty as distributions. Note that the distribution of variability gives you a fraction of a population; the distribution of uncertainty gives you the probability that you are wrong. In a probabilistic instead of deterministic calculation the numbers in the calculations are replaced with distributions. Difficulty of probabilistic analysis is conceptual: What do the distributions mean? Note that deterministic assessment ignores real life's complexity and is piling up conservative values. Sometimes deterministic assessments may be misleading, as you do not know the uncertainty in the outcome.

Probabilistic hazard characterization

In a dose response evaluation: the Point of Departure (PoD) is the dose where the effect is assumed to be small (NOAEL) or specified (BMDL). Note that the NOAEL is an imprecise estimate of BMDL. The next step is extrapolation: the PoD is translated to the equipotent dose in target population, using an interspecies assessment factor (consisting of uncertainty) and an intraspecies assessment factor (consisting of variability and uncertainty thereof).
For quantal data (only information is yes/no effect) the PoD is the dose with the effect in the average or typical animal. Here we cannot choose an effect size, the PoD can only be the ED50. In the case of quantal data the BMD10 reflects the variability in the animals used in the study, but since in animal testing we use animals that are the same as much as possible, this information is not relevant. In addition, the variability between animals does not say anything about variability in humans. We need human data to assess an intraspecies assessment factor.
A sensitive individual is defined as having a lower than average equipotent dose. Individuals may also be vulnerable: they are already at risk without exposure. IPRA defines individuals in the first sense, so as sensitive individuals: we want to protect everyone for the same effect size.

In practice:
Dose-response data: we accept all curves that fit the data. For each of the curves we calculate BMD, so we get BMD uncertainty distribution. We construct an interspecies (uncertainty) distribution based on historical data. Allometric dose-scaling is used to take into account body size differences. Creating a distribution for the *intra*species assessment factor is done as follows: the median is set to 1. This represents the average sensitive individual. The variability is defined by setting a high percentile of the distribution. Since this high percentile is uncertain the variability is defined by setting a lower and upper bound for the high percentile, e.g. of a factor 5 and 20.

Output of IPRA
Key quantities of IPRA are the degree/severity of the effect, the fraction of the population with that degree of effect and the uncertainty (coverage = level of conservatism). The Individual Margin of Exposure (IMoE) distribution is calculated by dividing the Individual Bench Mark Dose distribution by the Individual Exposure distribution. The fraction of population that has an IMoE <1 is the fraction that is affected. Of course the output of IPRA is also the uncertainty distribution around IMoE.

2.4 Bas Bokkers: case study DON

Bas Bokkers demonstrated how IPRA works in practice by showing the case study of deoxynivalenol (DON). Martin Paparella asked whether there are any other uncertainties that can be included in the probabilistic extrapolation factors. Wout Slob replied that additional uncertainties can be included, e.g. uncertainties in NOAEL can be quantified, or additional assessment factors when no developmental studies are available. Route-to-route extrapolation is more complex, if there are studies available.

Martin Paparella wanted to know if the experimental variability is interesting to include in IPRA? The answer was no: In animal studies the experimental

variability is made as small as possible. So the variability due to experimental differences is not interesting for IPRA (when you would use animals from different strains, there is more variation, which will lead to a less precise BMD). When BMDs studied in two labs are different, then it is interesting to look at. Because this gives an idea of uncertainty of BMD. The example of melamine was given, in which a 3-fold difference in two experiments was found.

Martin Paparella mentioned that in deriving probabilistic assessment factors using databases, 25% of the data cannot be used because they show qualitatively different responses (e.g. weight gain and weight loss in different species). Can you consider this in uncertainty analysis? Wout Slob replied that this is difficult. We cannot always trust the data; dosing errors etc. It is difficult to understand the differences (most of the times these are kidney effects which are different between rat and mouse). The best thing to do is to take as many data as you can get and take some distance from data, see the large patterns. Randomising a study is not as easy as it looks, and the noise will translate in the uncertainty of your assessment.

2.5 Discussion Day 1

It was concluded that the choice for showing a certain percentile (e.g. the 1st, as done in the examples today) does not need agreement between risk assessors. The choice of the percentile is a subject for discussion between risk assessors and risk managers. The participants agreed that as default the present percentiles are OK, and that this is a good way to visualize the output of IPRA. Lutz Edler warned to take care with the end of the whisker, which could perhaps be interpreted as an error bar. He suggested to use a star (asterisk) instead.

It was mentioned that one should be careful when MoEs are given numerically, as the interpretation is qualitative (e.g. MoE is safe when > 10000).

Gerhard Heinemeyer mentioned that IPRA is a very important step forward in risk assessment. But he noteed that the answer risk managers would want to get from a risk assessor is: 'Do you have a concern: y/n?' Probabilistic assessments do not give that answer. Furthermore, when the answer to this question would be yes, this would mean that the exposure should be reduced. Note that also the uncertainty (in relation to sensitivity) needs to be considered. Marcel Mengelers replied that IPRA shows, also on the hazard part, the contribution of the sources of uncertainty. So there could be efforts to reduce this uncertainty.

Lutz Edler asked whether it is not built in the 'IPRA system' that the uncertainty of the interspecies assessment factor is the most important. The answer was that indeed in many cases this is the most important source of uncertainty, but not in all. Bernard Bottex wondered if the interspecies uncertainty can be reduced at all. Bas Bokkers replied that this is the case, namely when you look specifically to kinetic differences between species in relation to a substance.

Marcel Mengelers asked whether you could play around with the data, perform a kind of sensitivity analysis by reducing the uncertainty and see how would that affect the bar/whisker plot? Wout Slob and Hilko van der Voet seemed to

disagree on the best answer to that. Text added later by Wout Slob: If you only reduce the width of the interspecies distribution, this addresses the question: what happens with the relative contribution of the interspecies uncertainty. If you want to know what the effect might be of spending resources in reducing the uncertainty in the interspecies extrapolation, the question is rather: Does this lead to the conclusion that risk is small? In that case not only the width but also the median of the distribution will change, and just reducing the width is wrong. Hilko van der Voet agrees on this. So performing a sensitivity analysis only makes sense when you keep in mind what question you can(not) answer.

Jean-Luc Volatier mentioned that two results are interesting: the IMoE percentile and its uncertainty. He thought it may be confusing to put two variables in one plot; perhaps it is better to plot the whole distribution together with uncertainty bands. Nevertheless with multiple toxicological endpoints this plot will become rather unreadable, then you would need a separate plot for every end point. Martin Paparella suggested that it would be helpful to get the distributions of the exposure and the BMD. Answer: This is already in the IPRA output.

Bernard Bottex put forward that a risk assessor would like to see more than one endpoint at once, whereas a risk manager would not.

Martin Paparella wondered whether the difference between non-threshold and threshold effects gets blurred? Wout Slob answered that the differences disappear, they do not get blurred.

3 Day 2: use, practicability and place of IPRA in risk assessment

3.1 Recapitulation of Day 1

Martine Bakker recapitulated Day 1, using some of the slides of Bas Bokkers of Day 1.

Alan Boobis suggested that the interspecies assessment factor should be considered as a distribution containing variability and uncertainty instead of uncertainty only. He explained that (multiple) species respond differently to the same dose (per kg bw), and thus there is existing, real world variation. It was replied that the interspecies factor should cover the difference in response between one particular animal species and human, and that this difference is often unknown, i.e. uncertain. Lutz Edler wondered if it is mostly a terminology thing, and emphasizes that assumptions should be made very clear!

What does 'individual' mean in the acronyms IMoE, IEXP, and IBMD? It means a random element, an anonymous person/person day. Note that a child that grows up becomes another individual. But not in chronic exposure where there may be accumulation over a lifetime, see the example of cadmium.

Hilko van der Voet asked whether the risk manager wants more information than the one uncertainty bar of the 1st percentile. Jacob van Klaveren replied that we should leave it to the risk manager to decide on the specific percentile. Alan Boobis added that in communication, we must give people the opportunity to feel comfortable with what we propose. We should compare the IPRA output with a classical (deterministic) RA.

3.2 Presentation of Bas Bokkers on bar plots of different IPRA studies

3.2.1 Bar and whisker plots of IMoE

DON: There is a large variability in the bars, possibly because the subpopulation is females in reproductive age. When they have a very small intake of DON, the bar will become very wide. On the other hand, a lot of staple foods contain DON, so it is not very likely that there is a very small or zero intake of DON.

Cd: In this case human toxicological data are used. Kidney effects are estimated for older people (>70 and >80 y); the uncertainty whiskers go below an IMoE of 1. There is no concern at 60 y. But note that Cd builds up in the body during lifetime, so prevention of exposure is also important at lower ages than 70 y. Alan Boobis asked: 'Not all present 5-year olds will become 80; you should use age-corrected morbidity?' The answer was no, because the output is a percentage of the surviving subpopulation of that age.

The usual intake calculated in this (and many other) cases is taken as a proxy, because we do not know the exposure over time and we assume that there is no change in exposure over time. Nevertheless in this case we use human data on accumulated Cd in the kidney, so we have historical data. Prediction for exposure in the future is possible for a scenario that the cadmium concentrations remain constant at a certain level over a longer period of time. The accumulation of Cd is taken into account by using a toxico-kinetic model.

Organophospate esters (OPs) / Acrylamide (non-carcinogenic effects) / Anti-androgenic pesticides:

When putting results of different toxicological end points in one plot: note that 5% body weight reduction may not be as adverse as a 5% reduction of red blood cells.

Bernard Bottex: 'Will these substances exceed the TDI in a deterministic assessment?' Wout Slob replied that those chemicals with exposure close to TDI were selected for the case studies at RIVM, so for this reason IMoEs of these substances are relatively low.

In the examples of OPs and acrylamide IMoEs are calculated for the Dutch population, but also other food consumption surveys can be uploaded. Also note that the time period for which the exposure was calculated for acrylamide was 2007, since then the exposure has been reduced.

When comparing assessments between countries: if you see different exposures, you want to know if this is a real difference or if the uncertainty is high. In probabilistic assessment you can make that visible.

Wout Slob added that when a bar is very wide, when you make an error in the 1st percentile this makes a big difference, when the bar is narrow an error has less impact on the value of the IMoE.

When the whiskers are very long they may overlap! Then there is not much info in the variability in the population. The width of the bar tells you something about variability in population, which is useful.

It is advised to not go lower than the 1st percentile, because then the uncertainty will increase much.

Martin Paparella believed that risk managers would like to know more practical numbers: mortality, or incidence, so the 'real' number of people per exposure level. Bas Bokkers replied that you can calculate the percentage of the population affected for each endpoint and subpopulation. If you know the size of subpopulations, you can calculate the number of persons affected.

Alan Boobis wondered if an IMoE < 1 automatically is a problem? The answer is yes, people get the response corresponding to the BMD or more (at left hand side). Bas Bokkers suggested to plot multiple effect sizes (e.g. 5, 10, and 15 % body weight reduction) to see how the bars shift.

Alan Boobis proposed to go to other scientists to ask in what way the results should be presented.

Wout Slob asked if it may be useful to have software that enables risk managers to choose in what manner to present the results. The group agreed with this.

Bas Bokkers warned to take care when comparing different effects between and within cases, as there may be different subpopulations and different effect sizes. As for the latter: are they equally adverse? (same problem as in deterministic approaches), in addition, the severity of some quantal effects is unknown (e.g. osteoporosis). Wout Slob: Histopathologists first look at the highest dose; the severity may be judged differently in different studies. Alan Boobis countered that there is some degree of science there.

3.2.2 Bar plots on the contributions of the different sources of uncertainty

Bas Bokkers explained that when the uncertainty originating from the Monte Carlo (MC) runs starts contributing, then there were too few runs done, the number of runs should have been higher.

Rob asked about not quantified uncertainties, are they included in the plot? The answer was no, they are not. Using expert opinions, you may replace the lack of data by data from experts.

Information on the uncertainty of intraspecies is obtained from published papers using farmaceutical data. But data are restricted to some subpopulations. So far we have matched the assessment factors with the currently used factor of 10. We applied intraspecies uncertainty but it does not (or hardly) come up in many bar plots.

Martin Paparella: Is it possible to add other uncertainties? Hilko van der Voet mentioned that they are developing this at the moment with FERA.

Alan Boobis: Is the uncertainty in the consumption always low? No, but compounds were selected that we had exposure information on.

Cadmium: Even with the human data the uncertainty in the intraspecies factor showed a large contribution to the total uncertainty, so this is very hard to reduce.

Interpretation of large uncertainty in BMD: There are many curves that fit the data, so dose-response data were poor (90% confidence interval is taken into account in the calculations).

3.3 Discussion Day 2

Rob Theelen posed two possible questions of risk managers and society:

1. **Acceptance:** Is IPRA approach in general supported by (all) risk assessors? Different visions are not preferred from the perspective of the risk manager.

Jacob van Klaveren stated that he hears a lot of support for the tool around the table. Martin Paparella mentioned that the risk manager will need to decide based on both risk and other interests (economic, societal) and alternatives and in some cases benefits, which is broader than risk assessment alone. Marcel Mengelers: 'Risk assessors still have discussions on the choice of toxicological endpoints, the value of assessment factors, etc. in deterministic assessments as well'. Gerhard Heinemeyer agreed, said that there is (and will be) a distribution of opinions. Rob Theelen urged that the risk manager will ask for one type of approach that all risk assessors are supporting. The reply of Wout Slob was that IPRA is not a different method, it is a higher tier method which refines the present approach. Bernard Bottex mentioned that when you document assumptions and choices in a transparent way, risk assessments using IPRA will be accepted by the risk assessor community.
Rob Theelen turned the question around: what cases would a risk assessor assess with IPRA? Martin Paparella proposed to decide case-by-case. For specific situations, perform IPRA, and show to other risk assessors to create engagement. Alan Boobis: 'We need greater engagement, also from the non-enthusiasts. This will likely take about 5 years'. Wout Slob put forward to apply IPRA when ADIs are exceeded (as a first step in getting IPRA accepted), as a higher tier calculation. Then nobody can say that it is 'the wrong way'.

Hilko van der Voet: 'What would be the best platform to discuss IPRA?' Bernard proposed the EFSA platform. Gerhard Heinemeyer claimed that more than one platform is needed: EFSA, ICPS, WHO and explains that we will need to start with using the network of this group. Martin Paparella added to try to bring on board the (experimental) model developers (large screening batteries of in vitro tests, they have own ideas on uncertainty). Rob Theelen thought it best to take it step by step: First national, then European, then global. Lutz Edler disagreed with this: Already some national agencies work with probabilistic methods, when a few countries are in favour then it is sufficient to go to the European level. Bernard Bottex agreed and proposed to put the national and European level in parallel.

By the way, there is already a WHO activity going on. There will be a (larger than this) workshop in June, at RIVM, with participants from Europe, US, and others, probably including some of the present IPRA participants.
Bernard wondered how applicable the tool could become for use in future international risk assessment practices. Jacob van Klaveren answered that due to the ETUI project (commissioned by EFSA) MCRA is fully connected to the EFSA comprehensive database for the exposure assessment part. Hilko van der Voet indicated that IPRA will become part of the MCRA toolbox. Consequently, IPRA can also be applied at EFSA level at the time MCRA version 8 will be released, provided that Hilko van der Voet will get some support for finalising the integration of these risk assessment tools. Then different Member States can apply IPRA provided they have access to (or ownership of) the required consumption (and toxicological) data. Additional training might be needed or might come from the AFSCO training course sponsored by EFSA.

Marcel Mengelers asked how we should expand our small network. Gerhard Heinemeyer replied that different national authorities may work together to convince their own colleagues, so the national level can be skipped. He added that we should not focus on just one tool; it is good to look from different

angles. Rob Theelen brought into mind that the national level is also NGOs such as consumer's organizations.

Conclusion:
IPRA should be put forward as a tool for higher tier risk assessment, rather than a completely different method from what is presently being used. And while there may be different opinions on details such as the choice of specific distributions for assessment factors (similar to the present discussion on the choice of their values in the deterministic methods), the general opinion of the participants on the use of IPRA is a positive one. This group should become larger: Our small network, arisen from this workshop, should engage their colleagues; try to enthusiast people at national, and in parallel at European level.

2. **Safe dose**. In the present methods, when exposure exceeds the ADI, then there is a need for measures. Rob Theelen's question: 'What is the safe dose in IPRA?'

Hilko van der Voet proposed to learn from nutritionists, who consider two cases: population (a minimal amount of nutrients needed for the population) vs. individual level (what is an adequate dose for the individual). IPRA relates to the population as a whole, considering safe dose having a variability. When you are talking about risks, you can give the number of people at risk.

Marcel Mengelers: 'Action is needed when an ADI is exceeded; but what kind of action? When exposure exceeds the ADI, in this case exposure can also relate to very few consumers'. Alan Boobis said that within EFSA there is an agreed way of expressing exposure: Mean and high level exposure. Martin Paparella mentioned that we should give the information to the risk manager in practical numbers (number of consumers at risk, what effect). This can be done with IPRA and is one of the benefits of the method.

Does exposure need to exceed the ADI to go to the next tier? Wout Slob replied that you will need to know the coverage (confidence level) of the assessment, to decide on the distance between exposure and ADI that is needed. Then you can decide when to take action. Gerhard Heinemeyer: 'You will have to identify the uncertainties, and perform additional studies to reduce them. Note that for the 99th percentile you need a lot of data to be rather certain'. Alan Boobis's reply was that more data are not always needed, another option would be a risk management restriction.

The benefit of IPRA is a more-informed decision tool. An added value will be that you can perform an IPRA before and after taking a specific measure and in this way it is possible to evaluate its result (e.g. when a maximum level in a product is reduced the effect of this measure on the exposure can be estimated).

Presently risk managers do not know what toxicological effect the ADI is based on. In IPRA you can show the uncertainty of the PoD. Alan Boobis: 'Risk assessors establish TDI from the critical effect, risk managers follow this. But to change this requires a change in communication'. Hilko van der Voet noted that ideally you would like to add up all relevant health effects.

And this complex information should be presented in a simple way to audience and risk managers. Wout Slob was of the opinion that consumers have representatives who can understand the principles of IPRA and said that they will come with the question: How sure are you that x% of the population is at risk? Rob Theelen wondered what happens if we could be sure that we have too strict ADIs.

Jacob van Klaveren opened the discussion that IPRA can even be more than a tool for refined assessment only. In combination with the probabilistic exposure modelling IPRA can also be a potentially useful tool in starting a discussion on the required level of protection of a population. As a consequence of new EU regulation we will enter a new time period in which we can expect many debates and developments related to cumulative and aggregated (multi-route) exposure. These developments might drive the need to reconsider our exposure assessment tools and the desired level of protection for all routes of exposure and all chemicals with a common toxic effect. After experience with these future tools we then can redesign risk mitigation measures for single chemicals and single routes. Alan Boobis supported that view and added new elements in that discussion to consider, such as sustainability and food security. It is Alan Boobis's opinion that we should increase the efficiency of risk assessments, because we will face more risk assessments to do, so we need a tiered system to accomplish this higher number.

Martin Paparella: 'If I would be able to organize a workshop for people of the in vitro testing methods, would you be interested in participating?' Hilko van der Voet said that this is one way of expanding the network and this could help to get more information on kinetics/dynamics as well. The aim of Martin Paparella would be to bring probabilistic thinking to the 'testing method community'.

Marcel Mengelers closed the discussion and concluded that IPRA, addressing both variability and uncertainty, appears to get acceptance among the people present and is sufficiently developed to bring IPRA further internationally. We as risk assessors think that we can convince risk managers that IPRA is a tool for refined, higher tier risk assessments. In communicating about IPRA, we should keep in mind that it is not a completely new method, and the tools are ready for use. We have already a small network in this workshop. If somebody may hear of relevant calls, workshops, projects, we recommend to contact this group. We felt sufficient enthusiasm to bring it further.

4 Conclusions

IPRA is a useful tool for higher tier risk assessments.

The (bar and) whisker plots of the Individual Margin of Exposure are a good way to visualize the output of IPRA.

The choice of a specific percentile to be presented in the (bar and) whisker plots (e.g. the 1st percentile, as in the examples of the workshop) is a subject for discussion between risk assessors and risk managers.

It may be useful to have software that enables risk managers to choose in what manner to present the results.

The small network, arisen from this workshop, should engage their colleagues and try to enthuse people at national, and in parallel at European, level.

Appendix 1 **Programme of the workshop**

Date: 12-13 December 2012
Venue: Netherlands Food and Consumer Product Safety Authority (NVWA). Utrecht, Catharijnesingel 59.

Wednesday 12 December
Chair: Rob Theelen

Time	**Subject**	**Speaker**
13.30 – 13.45	Welcome	Hub Noteborn
13.45 – 14.00	Introduction to the workshop: from probabilistic exposure assessment to IPRA	Jacob van Klaveren
14.00– 14.15	Demonstration of MCRA	Hilko van der Voet
14.15 –15.00	Principles of IPRA	Wout Slob
Tea		
15.30 – 16.15	Case studies	Bas Bokkers
16.15 – 17.00	Discussion	Marcel Mengelers

Thursday 13 December
Chair: Marcel Mengelers

Time	**Subject**	**Speaker**
9.30 – 9.45	Feedback of yesterday; time for questions	Martine Bakker
9.45 – 9.55	Results of IPRA: bar plots	Bas Bokkers
9.55-10.45	Discussion, part 1	Rob Theelen
Coffee		
11.15– 12.15	Discussion part 2 and conclusions	Rob Theelen

Appendix 2 **List of participants**

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