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B.G.H. Bokkers et al.

The practicability of the integrated probabilistic risk assessment approach for substances in food

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The practicability of the integrated probabilistic risk assessment (IPRA) approach for substances in food

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This investigation has been performed by order and for the account of the Food and Consumer Product Safety Authority (VWA), within the framework of project 'Risk assessment in case of exceeding health limits'

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Abstract

The practicability of the integrated probabilistic risk assessment (IPRA) approach for substances in food

In the Netherlands, the National Institute for Public Health and the Environment (RIVM) has successfully applied the IPRA approach to assess the human health risks of five substances in food. This method has been developed so that health risks can be described in more detail when a classical risk assessment has shown either that there is a risk or a risk cannot be excluded. Using the IPRA approach enables more information to be gained on the fraction of the affected population in relation to the severity of the effect. Based on this information, authorities can then take targeted measures to prevent any risk to human health. It is expected that the IPRA methodology will be suitable for use with other substances.

The above has been concluded from research performed by the RIVM in collaboration with Biometris and RIKILT – organizations that fall under Wageningen University and Research Centre. The research was commissioned by the Dutch Food and Consumer Product Safety Authority (VWA)

In the present study, the risks of two mycotoxins (DON and T-2/HT-2), one heavy metal (cadmium), one group of pesticides (OPs), and one compound (acrylamide) which is formed during the heating of food containing high levels of starch are described. The IPRA approach enables the amount of a substance with which a population is exposed to that substance through food to be compared with the maximum safe level. Differences between individuals and possible calculation errors have been accounted for. The IPRA showed that the exposure of the five substances studied was below the levels considered safe. The health risks can therefore be considered negligible.

Furthermore, the method can provide more insight on which additional information could be gathered in order to improve the risk assessment. This would help targeted follow-up research to take place.

Key words: probabilistic risk assessment, exposure, toxicological effect, extrapolation factor, benchmark dose

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Rapport in het kort

De bruikbaarheid van een geïntegreerde probabilistische (IPRA) methodiek voor de risicobeoordeling van stoffen in voeding.

Het RIVM heeft de IPRA-methode succesvol toegepast om de gezondheidsrisico's voor de mens van vijf stoffen in voeding te beschrijven. Deze methode is ontwikkeld om de risico's gedetailleerd te kunnen beschrijven als uit klassieke risicobeoordelingen blijkt dat er risico's zijn, of als risico's voor de gezondheid niet uitgesloten kunnen worden. Met de IPRA-methode is het mogelijk om aan te geven welk deel van de bevolking risico loopt nadat zij aan stoffen is blootgesteld en hoe ernstig de effecten op de gezondheid zijn. Op basis van deze informatie kan de overheid vervolgens doelgerichte acties ondernemen om de schadelijke gezondheidseffecten te voorkomen. Verwacht wordt dat de methode ook voor andere stoffen bruikbaar is.

Dit blijkt uit onderzoek van het RIVM in samenwerking met Biometris en RIKILT, beide onderdeel van Wageningen Universiteit en Researchcentrum. Het onderzoek is uitgevoerd in opdracht van de Voedsel en Waren Autoriteit (VWA).

Voor het onderzoek zijn de risico's beschreven van twee schimmeltoxinen (DON en T-2/HT-2), één zwaar metaal (cadmium), één bestrijdingsmiddelengroep (OPs) en één stof die in verhitte zetmeelproducten voorkomt (acrylamide). Met behulp van de IPRA-methode wordt de hoeveelheid van een stof die een populatie via voedsel binnenkrijgt vergeleken met de maximale dosis die veilig wordt geacht. Verschillen tussen personen en onzekerheden in de berekeningen zijn hierin meegenomen. De blootstellingen van deze vijf stoffen blijven volgens de methode onder de gestelde grenzen, en dus zijn de gezondheidrisico's verwaarloosbaar.

Verder kan met de methode inzichtelijk worden gemaakt welke aanvullende gegevens verzameld kunnen worden om de risicobeoordeling te verbeteren. Hierdoor is doelgericht vervolgonderzoek mogelijk.

Trefwoorden: probabilistische risicobeoordeling, blootstelling, toxisch effect, extrapolatie factor, benchmark dose

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Preface

We like to thank Waldo de Boer (Biometris) for programming the exposure component of the IPRA-software.

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Samenvatting

In dit rapport wordt de toepasbaarheid van de geïntegreerde probabilistische risicobeoordelings-methodiek (IPRA), beschreven door Van der Voet en Slob (2007), beoordeeld aan de hand van vijf stoffen. Het gebruik van een probabilistische aanpak voorziet in meer inzicht in de fractie van de populatie die een risico loopt in relatie tot de ernst van het toxicologische effect.

De risicobeoordelingen van vijf voorbeeldstoffen (DON, cadmium, OPs, T-2/HT-2 en acrylamide) werden met succes uitgevoerd. Toxiciteit- en blootstellingsdata waren beschikbaar in voldoende detail om de probabilistische risicobeoordelingsmethodiek toe te passen. Verwacht wordt dat ook de risico's van andere stoffen goed in kaart gebracht kunnen worden met deze methode, ook als er minder informatie aanwezig is om alle verdelingen af te leiden die ten grondslag liggen aan de risicobeoordeling. In dat geval kunnen deterministische waarden worden gebruikt om als invoer te dienen in het IPRA-(software)programma.

Deze studie onderstreept de noodzaak voor een nauwe interactie tussen toxicologen, blootstellingsexperts, risicobeoordelaars en risicomanagers. Zij dienen overeen te komen voor welke populatie de risicobeoordeling wordt uitgevoerd, en hoe de resultaten worden gerapporteerd. Verder vereist het vergelijken van potentiële gezondheidsrisico's van de blootstelling aan verschillende stoffen samenwerking tussen de experts. Het vergelijken van de risico's voor gezondheid door verschillende stoffen kan bijzonder bruikbaar zijn om te bepalen welke vervolgstudies of risicobeheersingsmaatregelen het best kunnen worden uitgevoerd.

In de gebruikte probabilistische risicobeoordelingsmethodiek kunnen bronnen van (kwantitatieve) onzekerheid worden geanalyseerd om inzicht te verkrijgen over hun relatieve bijdrage aan de totale onzekerheid in de resultaten van de risicobeoordeling. Deze informatie is zeer bruikbaar om te bepalen welke bron(nen) van onzekerheid kan worden aangepakt om de totale onzekerheid in de resultaten effectief te verminderen.

Naast de bronnen van onzekerheid die in de IPRA-software worden beschouwd, zijn er meer onzekerheden die van belang zouden kunnen zijn. Het wordt aanbevolen om zo veel mogelijk van deze bronnen te identificeren en te kwantificeren. Het is echter onpraktisch en onnodig om een zeer gedetailleerde onzekerheidsanalyses uit te voeren bij elke risicobeoordeling. De mate van detail van de onzekerheidsanalyse moet in perspectief staan tot de behoefte van de risicoschatting.

Een methode om de risico's van carcinogene stoffen te beschrijven is niet opgenomen in de huidige probabilistische aanpak. Het wordt aanbevolen dat de probabilistische risicobeoordelingsmethodiek wordt uitgebreid om dit mogelijk te maken. Naast dat het waardevol is om de risico's van carcinogene effecten te kunnen schatten, kan deze uitbreiding risicomanagers helpen bij het vergelijken van de risico's op carcinogene en niet-carcinogene effecten.

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Summary

In the present report risk assessments are performed for five compounds with the aim of assessing the applicability and feasibility of the integrated probabilistic risk assessment (IPRA) methodology as described by Van der Voet and Slob (2007). By applying this probabilistic approach more insight is gained on the fraction of the affected population in relation to the severity of the effect.

For each of the five example cases (DON, cadmium, OPs, T-2/HT-2, and acrylamide) the risk assessment could be performed with success. Toxicological and exposure data were available in sufficient detail for these compounds to apply the probabilistic risk assessment methodology.
It is expected that probabilistic risk assessments for other compounds are feasible just as well, even when the available data cannot provide all underlying distributions. For instance, when only summary data are available, the required input can also be incorporated in the IPRA software as deterministic values.

The current project emphasizes the need of a close interaction between toxicologists, exposure experts, risk assessors, and risk managers. They need to agree upon the definition of the target (sub)population, and the way outcomes should be reported. Furthermore, the comparison of potential health risks related to different compounds or effects requires collaboration between experts. The comparison of health risks associated with different compounds or effects can be particularly useful in establishing priorities for further studies or risk reduction measures.

In the probabilistic risk assessment methodology sources of uncertainty can be quantitatively evaluated to get a complete view of their relative contribution to the overall uncertainty in the final outcome of the risk assessment. This information can be used as an indication which source(s) of uncertainty should be addressed in further research to effectively reduce the overall uncertainty in the results.

There are numerous sources of uncertainty that are not taken into account in the IPRA software. It is recommended that these sources of uncertainty are identified and quantified as much as possible. However, it is neither practical nor necessary to conduct the most detailed uncertainty analysis in every risk assessment. The level of detail in the uncertainty analysis should be in line with the needs of the risk assessment.

A methodology to assess carcinogenic effects is not implemented in the current probabilistic approach. It is advised to extend the probabilistic risk assessment methodology such that it can handle carcinogenic effects as well. Apart from being valuable on its own, this would also improve the possibilities for risk managers to compare the magnitude of the risks between cancer and non-cancer effects.

1 Introduction

In risk assessment the exposure to compounds below a health-based limit value is generally regarded as being without appreciable risk of adverse human health effects. However, when exposure exceeds the health-based limit value it is unclear how severe the (adverse) effects might be and what fraction of the population might be affected (Slob, 2006b). The usual conclusion in such situations is that health effects in the human population cannot be excluded. Van der Voet and Slob (2007) recently developed an integrated probabilistic risk assessment methodology that may give a better answer to the question of how large the risk might be for a given exposure situation. Furthermore, the approach facilitates a thorough analysis of the uncertainties encountered in the risk assessment of compounds. This analysis enables a purposive reduction of the uncertainty in the risk assessment. It clearly indicates which uncertainty(/ies) should be addressed (in further research) to effectively reduce the uncertainty in the risk estimates.

1.1 Integrated probabilistic risk assessment

The general approach in risk assessment is deterministic: single values for exposure and for the health-based limit value are derived. To avoid adverse human health effects, variability and uncertainty are dealt with by making conservative estimates for these two values. A deterministic approach is suitable as a first tier approach: it may indicate that even in a worst-case scenario no appreciable 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.

A more realistic assessment includes the description of the variability and/or uncertainty in the parameters that underlie the risk assessment. Variability is an intrinsic property of a population, while uncertainty results from a lack of knowledge. The latter may be reduced by collecting more information. Both variability and uncertainty may be described by statistical distributions. These variability and uncertainty distributions can be integrated in a probabilistic risk assessment.

In the integrated probabilistic risk assessment (IPRA) method, as developed by Van der Voet and Slob (2007), two distributions are estimated: one for the individual human exposure (IEXP), and one for the individual (human) ‘critical effect’ dose (ICED). The human ICED is the hypothetical dose above which an individual will show a particular predefined effect. It is assumed that the human ICED varies among individuals, resulting in a distribution of human ICEDs which can be estimated from dose-response data and additional assumptions. From the combination of the human IEXP distribution and the human ICED distribution the fraction of individuals with an exposure exceeding their own ICED is derived. This fraction may be used as a measure of the health risk, given a particular adverse health effect, in the population.

1.2 Aim of this report

In the present report risk assessments are performed for five compounds with the aim to assess the applicability and the feasibility of the probabilistic risk assessment methodology as described by Van der Voet and Slob (2007). The five compounds are described below.

Methods on how to derive the human ICED distribution, human IEXP distribution, and the actual risk of the five compounds are described in chapters 2, 3, and 4, respectively.
Apart from estimating the risk, and its associated uncertainty, the relative contributions from the various uncertainties of the model inputs will be evaluated for each example compound. This is described in chapter 4. Finally, the applicability of the probabilistic risk assessment methodology is discussed in chapter 5.

1.3 Selected compounds

In previous reports (Bakker et al., 2008; Bakker and Janer, 2007) the selection of the five compounds as case studies for a probabilistic risk assessment is described. The selected compounds are: deoxynivalenol, cadmium, organophosphorus insecticides, T-2/HT-2, and acrylamide.

Deoxynivalenol
Deoxynivalenol (DON) is a mycotoxin belonging to the trichothecenes, a family of closely related compounds. This mycotoxin is produced by several plant pathogenic fungi, of which the *Fusarium* genus is the most important. The geographical distribution of the *Fusarium* genus appears to be related to temperature. DON is one of the most common mycotoxins found in cereals and grains such as barley, maize, oats, rice, rye, wheat. When ingested in high doses by agricultural animals it causes nausea, vomiting, and diarrhea. Therefore DON is sometimes called vomitoxin or food refusal factor (Bennett and Klich, 2003; JECFA, 2001). For DON two tolerable daily intake (TDI) values have been derived. RIVM, SCF and JECFA allocated a TDI for DON of 1 µg/kg bw/d. The Health Council of the Netherlands (GR, 2001) derived a TDI of 0.5 µg/kg bw/d. Reduced body weight gain is considered to be the critical effect of DON.

Cadmium
Cadmium is a heavy metal that accumulates in the body, where it gives rise to a number of adverse health effects. According to a recent intake estimation for cadmium (Baars and Van Donkersgoed, 2005), the whole Dutch population has an intake below the TDI of 7 µg/kg bw/week established by JECFA (JECFA, 2004). However, based on indications that this limit is not completely protective for a small part of the considered population, RIVM proposed a lower value for the TDI, i.e. 3.5 µg/kg bw/week (Baars et al., 2001). In a previous analysis, it was shown that this limit is exceeded by ~10 % of the Dutch children aged 1-6 years (Baars and Van Donkersgoed, 2005). The EU derived an acceptable chronic cadmium body burden of 0.7 µg Cd/gram creatinine in urine based on the extensive toxicological and epidemiological literature.

OPs
Organophosphorus insecticides (OPs) are a group of pesticides which have a common mechanism of action: inhibition of acetylcholinesterase (AChE), resulting in a spectrum of acute cholinergic effects (Mileson et al., 1998; Pope, 1999). Daily exposure to doses of several OPs, that by themselves may not

be a cause for concern, could cumulatively amount to an adverse health effect. To address the risk of exposure to this group of compounds, the exposures to the individual compounds should be addressed simultaneously. JMPR (2005) established an acute reference dose (ARfD) of 100 µg/kg bw/day.

T-2/HT-2
T-2 (CAS no.: 21259-20-1) and HT-2 (CAS no.: 26934-87-2) are mycotoxins of the group trichothecenes produced by fungi of the *Fusarium* genus, which are commonly found in various cereal crops and processed grains. T-2 and HT-2 often occur together in infected cereals. The fungi producing trichothecenes are soil fungi and are important plant pathogens which grow on the crop in the field (SCF, 2001). As T-2 is readily metabolized to HT-2, these two mycotoxins are evaluated together. T-2/HT-2 is mainly known to cause immunotoxicity and haematotoxicity (Bondy and Pestka, 2000; Parent-Massin, 2004; Rukmini et al., 1980; Smith et al., 1994). However, other effects have been reported as well. For an elaborate overview of the effects of T-2/HT-2 the reader is referred to reports by JECFA, SCF, and RIVM (JECFA, 2001; SCF, 2001; Wijnands and Van Leusden, 2000). The immuno- and haematotoxic effects are present at the molecular (antibody production), cell (red/ white blood cell), and organ (spleen, thymus) level. The provisional maximum TDI for T-2/HT-2 is based on a study of Rafai et al. (1995) who show effects in pigs at the lowest dose tested (0.03 mg/kg bw) after 3 weeks exposure. Meissonnier et al. (2008) performed a similar experiment confirming the effects on the immune response.

Acrylamide
Acrylamide was first detected in foods heated at high temperatures in Sweden in 2002 (Tareke et al., 2002), Presence of acrylamide in food caused a worldwide concern, due to the classification of acrylamide as a group 2a carcinogen (IARC, 1994). However, this classification is under debate (Besaratinia and Pfeifer, 2007; Gargas et al., 2009; Wilson et al., 2006). Research showed that acrylamide can be formed by heating of many starchy foods, like French fries, biscuits and crisps. The compound is formed in the Maillard reaction (Mottram et al., 2002; Stadler et al., 2002). The reaction only occurs at temperatures above 100°C (Friedman, 2003).
Since the detection of acrylamide, numerous actions have been, and are still, undertaken to reduce acrylamide concentrations in food. Reducing measures focus on several aspects, like changing the baking agent, heating advices, and selection of potato cultivar (Dybing et al., 2005; Stadler and Scholz, 2004). The Confederation of the Food and Drink Industries in the EU has developed an approach, which provides a way to help food manufacturers to identify approaches to help control acrylamide in different types of foods. For example, several studies demonstrated that reducing temperatures during frying resulted in lower acrylamide concentrations in potato products (Rydberg et al., 2003; Tareke et al., 2002; Taubert et al., 2004). Also the use of a different baking agent resulted in a reduction of acrylamide concentrations by more than 60 % in gingerbread (Amrein et al., 2004).
In experimental animals, acrylamide is rapidly and extensively absorbed from the gastrointestinal tract following oral administration. The pivotal effects of acrylamide in humans are neurotoxicity, reproductive toxicity, and carcinogenicity (Dybing and Sanner, 2003; EFSA, 2005, 2008; Exon, 2006; JECFA, 2005; SCF, 2002). Health-based limit values for both neurotoxicity and carcinogenity have not been derived due to the rather weak database.

Acrylamide was evaluated by the International Agency for Research on Cancer (IARC) in 1994 and classified as ‘probably carcinogenic to humans’ (IARC Group 2A) on the basis of a positive cancer bioassay result, supported by evidence that acrylamide is efficiently biotransformed into a chemically reactive genotoxic metabolite, GA, in both rodents and humans (IARC, 1994). However, epidemiological studies carried out in recent years on the general population have produced inconsistent results concerning carcinogenicity. On the basis of these data EFSA (2008) concluded that

the latest evaluation on acrylamide carried out by JECFA (2005) was still relevant and that there is currently no need to revise the risk assessment. However, additional new data are expected to become available in 2009-2010 that may call for revision of the risk assessment advice.

2 Effect characterization

Benchmark dose
A literature review was performed to identify the relevant effects for each example compound. For all five compounds quantitative dose-response data were found that were suitable for dose-response analysis.
Using PROAST (Slob, 2002) dose-response models were fitted to the toxicity data, and for each endpoint considered relevant a benchmark dose for a continuous response, i.e. a critical effect dose (CED), was derived. The CED is conceptually similar to the benchmark dose (BMD). However, it does not use the original definition for the BMR (benchmark response), i.e., a specific increase in incidence, at the population level. Instead, we use the critical effect size (CES) as the predefined change in response, which is defined at the individual level. In continuous endpoints, CES denotes a percent change in the continuous endpoint compared to the controls (Slob and Pieters, 1998). The CED associated with a particular CES relates to the average individual in the studied population. For example, the CED for acetylcholinesterase activity may correspond to a CES of 20 % decrease in acetylcholinesterase activity in the average animal relative to the average level in the controls.

Since the aim of IPRA is to evaluate various sensitive endpoints for each compound, and, in addition, to compare the results for these endpoints within and between compounds, it is necessary to define the CED for quantal endpoints in a way that such comparisons are, at least conceptually, possible. For that reason, in applying the benchmark dose approach to quantal dose-response data the estimated dose is derived where the average animal or human is going to show the effect, and this dose will serve as the CED. In this way, the CED for quantal data is analogous to the CED in continuous data. The difference between continuous and quantal data is that in continuous data CES can be specified at will, while in quantal data only one 'value' for CES can be evaluated: the CES that defines the difference between response and no-response. For instance, for the endpoint hematocrit we could estimate the CED associated with, say, CES = 5 %, 10 % or 20 % decrease, while for malformations the 'CES' is already defined by the endpoint considered

The uncertainty around a CED can be expressed by a confidence interval (Moerbeek et al., 2004). In the applied probabilistic risk assessment approach the whole uncertainty distribution around the CED is used as an input, which can be obtained by bootstrapping (Slob and Pieters, 1998).

Multiple models were fitted to the same data to account for model uncertainty. When a model is accepted (based on the log-likelihood criteria, see (Slob, 2002)) then the bootstrap technique (1000 runs) is used to generate a CED distribution for each accepted model. The distributions obtained for each of them are combined to generate an overall CED distribution.

Extrapolation
Generally, the experimental exposure scenario and the experimental population (often animal studies) are not (exactly) the same as the exposure scenario and the (human) population which the risk assessment is intended for. Therefore the CED (uncertainty distribution) derived from an experimental study cannot directly be used as an individual human CED (ICED) distribution. Hence, the CED distribution is divided by one or more extrapolation factor (EFs), which account for these differences, to derive the distribution of ICEDs. This distribution describes the interindividual variability in the target population (with uncertainty bands). In all five case studies interspecies and intraspecies

extrapolation is applied. Additionally, in one case study subacute-to-chronic extrapolation was required.

Interspecies extrapolation

According to its definition, a CED derived from an animal can be considered to relate to the average animal. Since the (average) animal is regarded as a model for the average human being, an interspecies EF is required to obtain the (average) human CED.
Interspecies extrapolation is performed in two steps: allometric scaling to account for interspecies differences in body weight (bw) and applying an EF for interspecies differences in kinetics and dynamics (Bokkers and Slob, 2007). To achieve allometric scaling the following factor is derived:

$$\left(\frac{mean\,human\,bw}{mean\,animal\,bw}\right)^{1-scaling\ power} \quad . \qquad (1)$$

This factor depends on the species used in the toxicological study, as well as on the human body weight in target population. Depending on the toxicological effect a (sub)population may contain one or both sexes or a particular age range. For example, when an effect is occurring in female rats of reproductive age then the mean body weight of women of reproductive age are used for the allometric scaling factor. When the toxicity studies indicate that there are no particular age groups at risk then the whole population (age 1-97, both sexes) can be used, or an age range can be chosen based on knowledge or hypotheses about the exposure (see chapter 3).

The (geometric) mean of the body weights instead of a distribution of body weights is used, because interspecies extrapolation is defined as extrapolation from the mean animal to the mean human. Variation in animal body weight is not relevant for human risk assessment and the variation in human body weight will be accounted for in the intraspecies extrapolation.
The allometric scaling power is assumed to be in the range of 0.65 to 0.75. To account for this uncertainty, the scaling power is described by a (normal) distribution with a mean of 0.7 and SD of 0.033. This SD is derived by assuming that the 5^{th} and 95^{th} percentiles of the distribution are 0.65 and 0.75, respectively.

The EF for interspecies differences in kinetics and dynamics is considered uncertain and is therefore implemented as a distribution. We assumed a lognormal EF distribution with a geometric mean (GM) of 1 and a geometric standard deviation (GSD) of 2, based on an extensive analysis comparing rat and mouse data from NTP studies (Bokkers and Slob, 2007).

Intraspecies extrapolation

By applying an intraspecies EF distribution a distribution of human ICEDs is obtained. The intraspecies EF accounts for the variability in sensitivity within the whole human population. The variability in sensitivity may be different for each effect considered. One way to quantify this variability, by expert judgment, is in terms of a factor between the 5^{th} and 50^{th} percentile of the distribution, reflecting by how much the CED of the sensitive 5 % of the population is lower than that of the average individual. This could be judged, for example, to be a factor lying somewhere between 2 and 10. This (uncertain) information can be translated into a lognormal distribution, in this example with GM = 1 and GSD = 1.9 for reflecting the variability, and an associated chi-squared distribution of 6.25 degrees of freedom for the GSD, reflecting the uncertainty in that assumed variability. For a detailed description of the construction of the intraspecies EF, see Van der Voet et al. (in press)

Subacute-to-chronic extrapolation

The subacute-to-chronic EF is described by a lognormal distribution with a GM of 4.1 and GSD of 4.4. This distribution was empirically derived from subacute and chronic data by Kramer et al. (1996).

2.1 Effect characterization DON

Benchmark dose(s)

A literature review was performed to identify toxicity studies with DON. The relevant effects induced by DON included reduced body weight, toxicity to male fertility, and developmental toxicity. Three studies evaluated effects on body weight. The CED obtained for this endpoint was lowest in the study by Iverson et al. (1995). Therefore, we only used the data from Iverson regarding the effects of DON on body weight. Table 1 summarizes the relevant endpoints, which are used for dose-response analysis. Furthermore, the CES and the best estimate CED are listed for each endpoint.

Table 1. Summary of the studies used to characterize the dose-response relationships for the effects of DON.

Species	Exposure	Doses (µg/kg bw/dy) (N per group)	Effect	CES	CED (µg/kg bw/dy)	Reference
Rat	28 days gavage	0.5, 1.0, 2.5, 5.0 (15)	Epididymal weight	-10 %	2.57	(Sprando et al., 2005)
			Seminal vesicle weight	-10 %	1.25	
			Testicular sperm count	-10 %	2.96	
			Germ cell degeneration	NA[a]	3.59	
			Failure of sperm release	NA[a]	2.31	
Rat	GD 6-19 gavage	0.5, 1.0, 2.5, 5.0 (24)	Fetal body weight	-5 %	1.23	(Collins et al., 2006)
Mouse	GD 8-11 gavage	0.5, 1.0, 2.5, 5, 10, 15 (15-19)	Resorptions	NA[a]	4.07	(Khera et al., 1982)
			Fetus anomalies	NA[a]	2.20	
Mouse	2 years diet	0.1, 0.5, 1.0 (50)	Body weight	-5 %	0.32	(Iverson et al., 1995)

[a] no CES is defined because of quantal endpoint

In Figure 1 the dose-response curve is given for the body weight against the dose DON. In this case an exponential model was fitted to the continuous data. As another model (Hill) is applicable too, the

distributions obtained from both models were combined to obtain an overall CED uncertainty distribution (Figure 2).

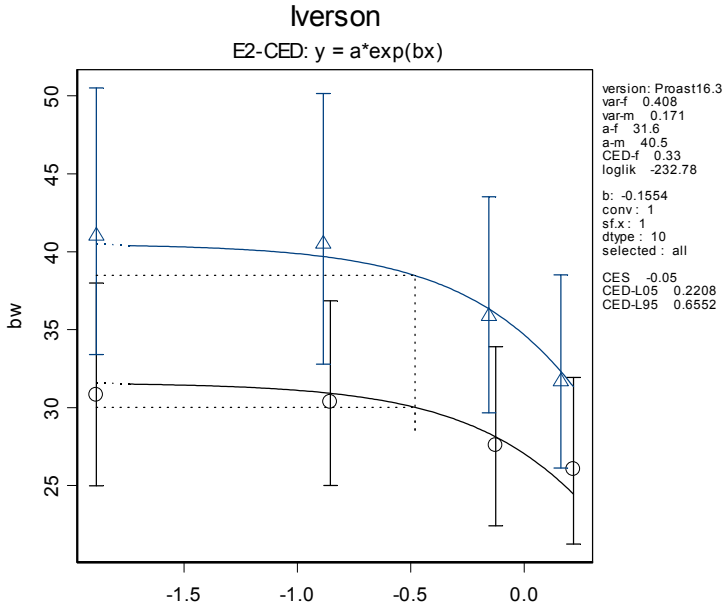


Figure 1. Dose-response of body weight (g) against log_{10}-dose (µg/kg bw/dy). The CED (vertical dotted line) corresponds to a CES of 5 % decrease in body weight (horizontal dotted line): triangles: males and circles: females. Data are from Iverson et al. (1995).

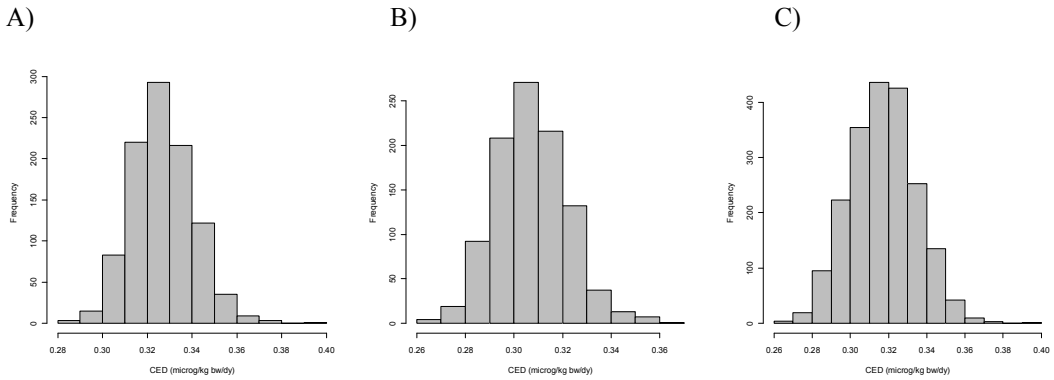


Figure 2. CED distributions corresponding to a 5 % decrease in body weight. A) The distribution obtained from an exponential model model (E2). B) The distribution obtained from the Hill model (H2). C) The CED distribution obtained from combining the 2000 estimates from both models.

Extrapolation factor(s)

The animal-derived CED distributions are extrapolated to the human situation using an interspecies and intraspecies extrapolation factor. In addition, a subacute-to-chronic EF is applied to the male

fertility effects (epididymal weight, seminal vesicle weight, testicular sperm count, germ cell degeneration, and failure of sperm release).
In Table 2 the animal and human body weights are shown that are used to derive the allometric factor (according to equation (1)). When available, the animal body weights are derived from the study reports, otherwise default body weights were applied. The body weights of the target populations are obtained from the Dutch National Food Consumption Survey of 1997/1998 (DNFCS-3, Kistemaker et al., 1998; Voedingscentrum, 1998).

In Table 3 an overview is given of the EF distributions used to extrapolate each effect to the human situation.
Integration of the CED and EF distributions in the probabilistic risk assessment will be described in chapter 5.

Table 2. Body weight of the tested and target populations.

Endpoint	Tested population			Target human population		
	Species	Sex	Mean bw	Age	Sex	Mean bw
All male fertility effects	Rat	M	337 g	15-45	M	80.9 kg
Fetal body weight	Rat	F	210 g	15-45	F	69.6 kg
Resorptions	Mouse	F	30 g	15-45	F	69.6 kg
Fetus anomalies	Mouse	F	30 g	15-45	F	69.6 kg
Body weight	Mouse	M & F	49 g	1-19	M & F	33.2 kg

Table 3. EF distributions (all lognormally distributed).

Effects	Allometric factor	Interspecies TK & TD	Subacute-to-chronic	P95 of intraspecies factor is between:	Intraspecies
All male fertility effects	GM=5.2 GSD=1.2	GM=1 GSD=2	GM=4.1 GSD=4.4	2-10	GM=1 GSD=1.9 df=6.25
Fetal body weight	GM=5.7 GSD=1.2	Ditto	--	Ditto	Ditto
Resorptions	GM=10.2 GSD=1.3	Ditto	--	Ditto	Ditto
Fetus anomalies	GM=10.2 GSD=1.3	Ditto	--	Ditto	Ditto
Body weight	GM=7.1 GSD=1.3	Ditto	--	Ditto	Ditto

2.2 Effect characterization cadmium

Benchmark dose(s)

Existing risk assessment reports (e.g., JECFA, 2004) and literature were reviewed to identify the relevant endpoints and studies of cadmium toxicity. Cadmium is known to induce kidney damage, increase blood pressure, increase bone fractures (or increase osteoporosis), to alter fertility, induce tumors and cause neurobehavioral alterations in experimental animal and/or human studies. Kidney effects, which are usually the basis for human risk assessments (see e.g., JECFA, 2004), and bone effects are the most deeply investigated cadmium effects. For these two endpoints, sufficient data to derive dose-response relationships were available. Table 4 summarizes the relevant endpoints, which are used for dose-response analysis. Furthermore, the CES and the best estimate CED are listed for each endpoint.

Table 4. Summary of the studies used to characterize the dose-response relationships for the effects of cadmium.

Species	Exposure	Doses (N per group)	Effect	CES	CED (µg/kg bw/day)	Reference
Rat	1 year, drinking water	0, 1, 5, 50 mg Cd/L (40)	Bone mineral density	-5 %	200	(Brzóska and Moniuszko-Jakoniuk, 2005b)
Human	Measured in urine (see text)		Osteoporosis	Additional risk +5 %[a]	17	(Alfvén et al., 2002; Jin et al., 2004; Nordberg and Kjellström, 1979)
			Kidney dysfunction	CES: 1000 µg β2-MG/g creatinine	Age 60-70: 17 Age 70-80: 6 Age 80-90: 4	(Gamo et al., 2006; Nordberg and Kjellström, 1979)

[a] the CED for the average human could not be derived for this quantal endpoint

Kidney effects

Extensive datasets exist for cadmium-induced kidney alterations in humans. The data gathered in a meta-analysis (Gamo et al., 2006) were used to derive a dose-response relationship and obtain CED distributions for the human population. This dose-response was based on urine cadmium concentrations as a measure of dose, and urine β2-microglobulin (β2-MG) as a biomarker of adverse effects in kidney. Kidney function deteriorates with age, and consequently β2-MG levels increase with age. Therefore, a certain percent increase in β2-MG levels has different health implications at different ages. For this reason, we used a cut-off point of 1000 µg β2-MG/g creatinine instead of a percent increase to derive the CED distributions. This critical level is somewhat arbitrary but has been considered in previous work as the cut off point associated with kidney dysfunction (Gamo et al., 2006).

To compare the CED distributions obtained with dietary exposure data, the urinary cadmium concentrations were extrapolated to cadmium intake. We used the toxicokinetic model for cadmium described by Nordberg and Kjellström (1979) to derive the relationship between urinary cadmium concentration and dietary intake for the different age groups considered in the study.

In Figure 3 the concentrations of the biomarker (β2-MG) in the urine are plotted against the urinary cadmium concentrations depending on age. The fit of the model did not improve by considering sex as a covariate.

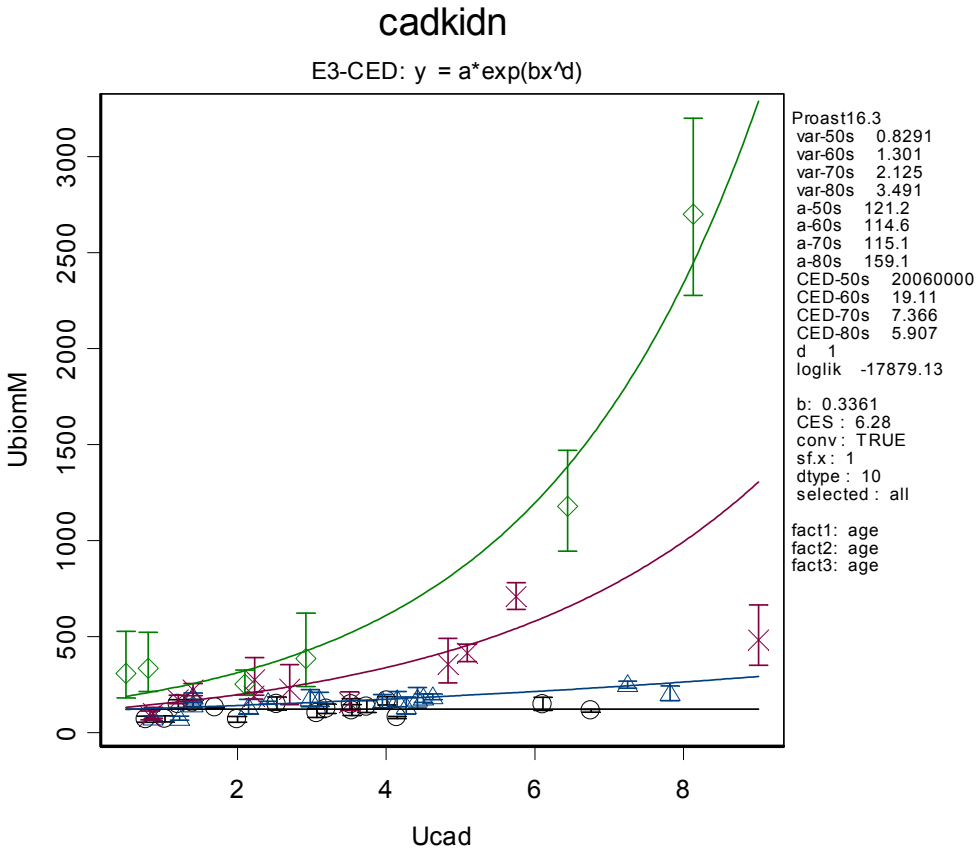


Figure 3. Modeled relationship between the urinary biomarker (in µg/g creatinine) and urinary cadmium concentrations (in µg/g creatinine) based on the epidemiological data reviewed in Gamo et al. (2006). Four age groups, 50-60 years, 60-70 years, 70-80 years, and 80-90 years are indicated by circles, triangles, crosses, and diamonds, respectively.

The models fitted to the data were used to estimate the CEDs that lead to the defined cut-off point of 1000 µg β2-MG/g creatinine for each age group. The distributions of CEDs obtained are shown in Figure 4. These values, expressed as cadmium concentrations in urine, were extrapolated to long-term dietary cadmium intake using the relation between intake and urinary excretion shown in Figure 5.
The best estimates (medians) of the derived CED distributions in terms of total dietary cadmium intake were: 17, 6, and 4 µg/kg bw/day for age group 60-70 years, 70-80 years, and 80-90 years, respectively.

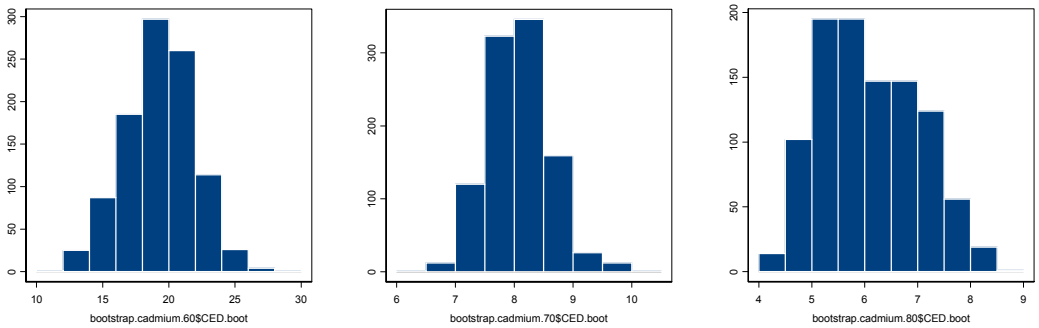


Figure 4. Uncertainty distributions of the dose (in terms of urine cadmium concentrations) that would lead to a urine β2-MG concentration of 1000 µg /g creatinine. From left to right: age group 60-70 years, 70-80 years, and 80-90 years.

Figure 5. Long-term oral cadmium intake vs. urinary cadmium excretion for different age-groups derived from the toxicokinetic model described by Nordberg and Kjellström (1979).

Bone effects

Several animal studies report dose-response data for the effects of cadmium on bone mineral density. We consider the chronic studies with male and female rats (Brzóska and Moniuszko-Jakoniuk, 2005a, b) the most relevant. These studies report the effects of cadmium on several endpoints (different measures of bone density and different bones), which showed a very similar response to cadmium exposure. Therefore, only bone mineral density in femur is used for the effect characterization. Females were considerably more sensitive than males and it was decided to limit the risk assessment to the female population (Figure 6). A dose-response model was fitted to the data. The CED distribution for a 5 % decrease in bone mineral density is derived (Figure 7). The CED distribution for the average female rat has a median of 200 µg/kg bw/day.

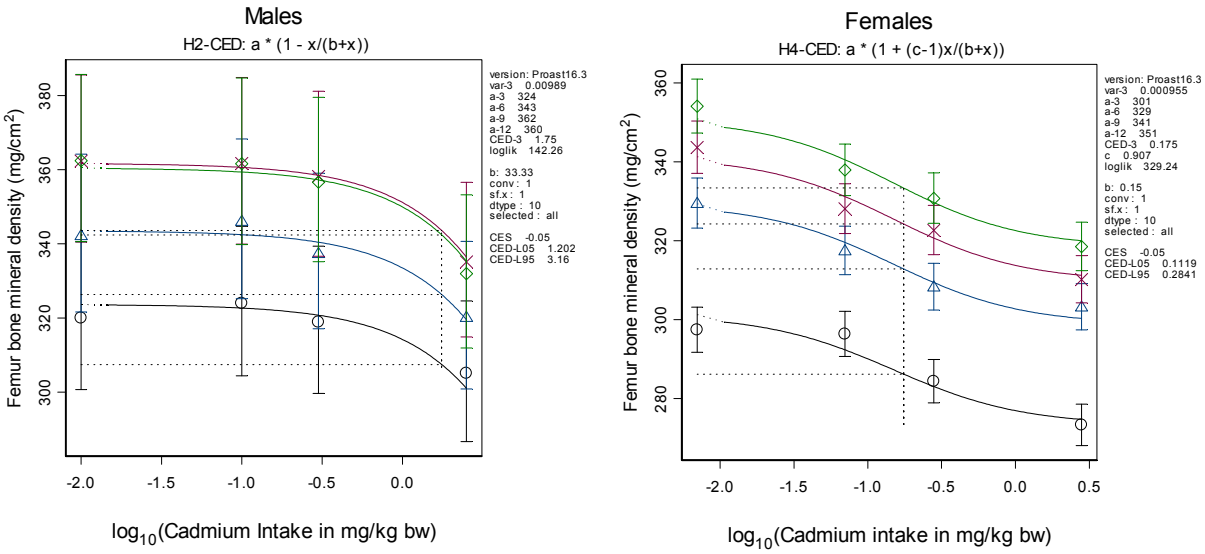


Figure 6. Dose-response for bone mineral density in femur (in mg/cm²) vs. $\log_{10}$ of cadmium intake (in mg/kg bw/day). The circles, triangles, crosses, and diamonds indicate the dose-responses at 3, 6, 9, and 12 months after the start of the study, respectively.

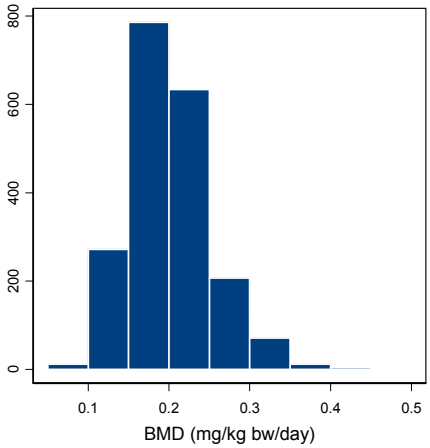


Figure 7. Uncertainty distribution for the dose associated with a 5 % decrease in femur bone mineral density in female rats.

Several human studies looking at bone effects exists. However, different endpoints were assessed and a meta-analysis similar to the one for kidney effects is therefore not feasible. We selected two epidemiological studies to see if the results as just derived from the rat data are not inconsistent with the findings in humans: Alfvén et al. (2002) and Jin et al. (2004). The first of these two studies was

also considered as the most relevant study by the EU RAR for cadmium effects on bones (EU, 2007). The second study allows the derivation of a dose-response relationship between urine cadmium concentrations and prevalence of osteoporosis for a general population environmentally exposed to cadmium in China.

The study by Alfvén et al. (2002) reported that people with blood cadmium concentrations between 5 and 10 nM have lower bone mineral densities compared to people with blood cadmium concentrations below 5 nM. The reported mean blood cadmium concentration in these two groups were 7.2 and 2.5 nM, respectively. The toxicokinetic model for cadmium described by Nordberg and Kjellström (1979) was used to derive the associated long-term cadmium intake. The blood concentration of 7.2 nM is associated to a long-term cadmium intake of approximately 2 μg/kg bw/day.

The study by Jin et al. (2004) reports the prevalence of osteoporosis in five subgroups of people with increasing urine cadmium concentrations. Dose-response models were fitted to these data and the dose associated to a 5 % increase in the prevalence of osteoporosis was derived (Figure 8). It may be noted that another option would be to follow an approach for quantal data that better matches the CES as defined for continuous data, as discussed in, e.g., Bos et al. (2009). Indeed, it may be argued that this approach is preferable for the purpose of comparing the final risk outcomes related to continuous vs. quantal data.

The urine concentration with a median of 17 μg cadmium per g creatinine associated to the 5 % increased incidence was extrapolated to a long-term cadmium intake using the toxicokinetic model for cadmium described by Nordberg and Kjellström (1979). This urine cadmium concentration is associated to a long-term cadmium intake of approximately 1.2 mg/kg bw/day.

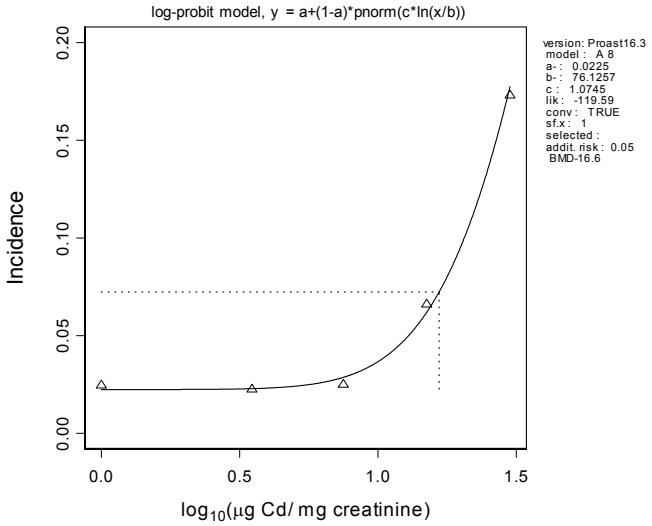


Figure 8. Dose-response for osteoporosis prevalence as a function of urinary cadmium concentration. Data are from Jin et al. (2004).

The two benchmark exposures in these two epidemiological studies are quite different. However, they are not directly comparable. First of all, osteoporosis may be regarded as a severe stage of low bone

mineral density (WHO, 2003). Therefore it is not surprising that the benchmark exposure is higher when obtained from an increased prevalence of osteoporosis as compared to being based on a statistically significant decrease in bone mineral density. Another reason for obtaining different benchmark exposures is the different experimental setup of the Jin and Alfvén studies: the biomarkers are measured in different matrixes (blood vs. urine) and different subpopulations (Swedish vs. Chinese).
The best estimate of the dose associated to a 5 % decrease in bone mineral density in the animal study is 200 µg/kg bw/day, which is in the range of the benchmark exposures derived from the human studies[1].

Extrapolation factor(s)
The rat derived CED distribution for bone mineral density is extrapolated to the human situation using an interspecies and intraspecies extrapolation factor.
In Table 5 the rat and human body weights are shown that are used to derive the allometric factor (according to equation (1)). The animal body weight is derived from the study report. The body weights of the target populations are obtained from DNFCS-3.
In Table 6 an overview is given of the applied EF distributions. The CED distributions for osteoporosis and kidney dysfunction are obtained from human studies. Therefore, no interspecies extrapolation is applied. The variances obtained when modeling the dose-response relationships for each of the age groups in the epidemiological data were used as an indication of the differences between sensitive and average humans. These values were considered as the upper bound of these possible differences because the experimental variances are likely to reflect other factors in addition to differences in sensitivity. The lower bound of these possible differences was estimated to be four-fold lower than the upper bound.

Integration of the CED and EF distributions in the probabilistic risk assessment will be described in chapter 5.

Table 5. Body weight of the tested and target populations.

Effect	Tested population			Target human population		
	Species	Sex	Mean bw (kg)	Age	Sex	Mean bw (kg)
Bone mineral density	Rat	F	0.35	15-20	F	61
Osteoporosis	Human (Asian)	M&F	56 kg	20-70	M&F	56 kg
Kidney dysfunction age group 60-70	Human	M&F	56 kg	20-70	M&F	56 kg
Kidney dysfunction age group 70-80	Human	M&F	56 kg	20-70	M&F	56 kg
Kidney dysfunction age group 80-90	Human	M&F	56 kg	20-70	M&F	56 kg

[1] Allometric scaling of 200 µg/kg bw from rat to human results in 40 µg/kg bw

Table 6. EF distributions (all lognormally distributed).

Effect	Allometric factor	Interspecies TK & TD	P95 of intraspecies factor is between:	Intraspecies
Bone mineral density	GM=4.7 GSD=1.2	GM=1 GSD=2	5-20	GM=1 GSD=3.6 df=21
Osteoporosis	--	--	5-20	GM=1 GSD=3.6 df=21
Kidney dysfunction at age 60-70	--	--	2-9	GM=1 GSD=1.9 df=6.7
Kidney dysfunction at age 70-80	--	--	4-17	GM=1 GSD=3.1 df=16
Kidney dysfunction at age 80-90	--	--	5-20	GM=1 GSD=3.6 df=21

2.3 Effect characterization OPs

Benchmark dose(s)
The critical effect under consideration is inhibition of AChE in the brain. This is a transient, reversible effect due to reactivation and *de novo* synthesis of AChE. The pattern of exposure (dose, composition and frequency) determines the time course of inhibition. It is not fully understood how the time course of inhibition relates to adverse symptoms of cholinergic crisis (peak, prolonged inhibition, or a combination of both), but it is generally assumed that inhibition below 20 % does not cause adverse symptoms. Therefore, the CES used here is a decrease of 20 % in brain AChE activity.

Residues of 30 different OPs have been found in samples of Dutch food items. For 15 of these OPs, dose response-data were provided by US EPA, mostly (semi)chronic repeated dose studies (Table 1), and for these 15 OPs we derived the CEDs. There is a discrepancy between animal and human exposure patterns: animals receive a constant daily dose of a single OP, whereas humans may be exposed irregularly to a variety of OPs. We made two conservative assumptions:

- All OPs ingested by humans on the same day are ingested at the same time.
- Dose-response data from repeated dose studies were used as surrogate for acute effects. We assumed that steady-state inhibition after repeated doses is not much higher than the maximum inhibition after exposure to a single dose.

For the remaining 15 OPs in the residue concentration database (those for which no EPA data were available), we obtained a point of departure from descriptions of toxicity studies in the JMPR monographs (2008), serving as a surrogate for the CED.

Relative Potency Factors
In the RPF approach, doses of all chemicals are expressed as equivalents of one of them: the index chemical. The effect of the combination equals that of the sum of the equivalents of the index chemical. This method requires:

- the same target/effect – it is assumed that OPs inhibit AChE by a common mechanism;
- no interactions between the chemicals – no clear evidence of interactions has been found in several mixture studies;
- parallel dose-response curves – this will be verified by analysis of dose-response data.

For the OPs for which we have dose-response data, parallel dose-response functions were fit to the data for all OPs simultaneously using the software PROAST (Slob, 2002).
The available dose-response data could indeed be described well by parallel dose-response curves (See below). The only exception was malathion, which appeared to have a more shallow dose-response. Its relative potency is however so low that the contribution to the cumulative effect may be negligible. This will be verified by the exposure assessment below.

In the toxicity studies some differences in sensitivity between males and females were observed. Overall, females appeared to be slightly more sensitive than males, but not consistently. No information is available showing that this difference is a true sex related effect relevant to humans. The female data are used to estimate RPFs and the CED of the index chemical. Methamidophos is used as the index OP. In theory, the arbitrary choice of the index chemical should not affect the results. Bosgra et al. (in press) confirmed this by repeating the calculations acephate as index OP.

The upper panel of Figure 9 shows the simultaneous fit of the dose-response curves related to the 15 OPs. There were considerable differences in background AChE levels between the studies (hence between the OPs). Data were re-scaled to the dose-response curve of methamidophos by correcting for differences in background AChE levels, resulting in the lower left panel in Figure 9. This results in this figure were used to estimate the RPFs. Next, the dose-response data were corrected for the differences in potency, i.e., the RPFs for each OP. This resulted in the lower tight panel of Figure 9, and from this analysis the distribution for the CED (at 20 % inhibition) for the index chemical was derived.

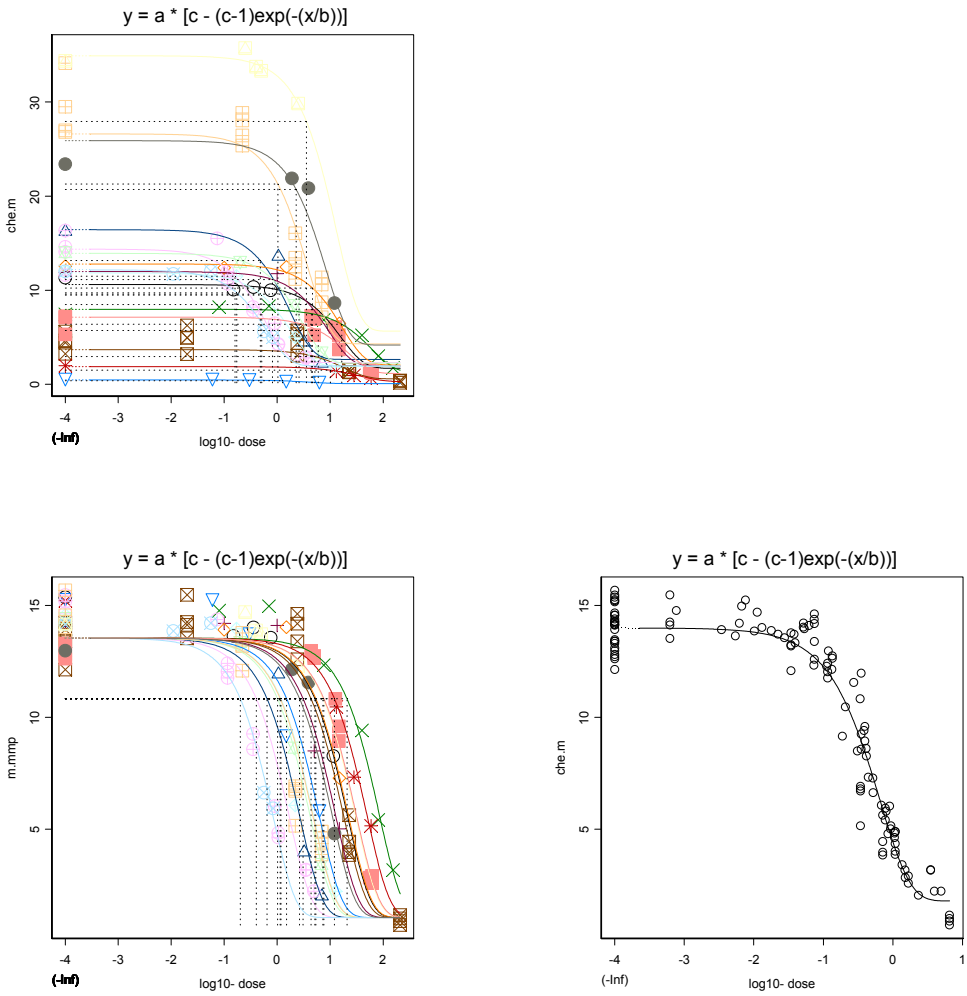


Figure 9. Upper panel: dose-response data of 15 OPs from the US EPA database described by the same fitted model, taking differences in background response and in potency into account (parameters a and b, respectively). Lower left panel: dose-response data vertically re-scaled to the background AChE level in the dataset of the index chemical (methamidophos). Lower right panel: data horizontally scaled by correcting for the relative potency of each OP.

Table 7. Summary of the studies used to characterize the dose-response relationships for the effect of AChE.

Species	Exposure	Doses (N per group)	Effect	CES	CED for the index chemical (µg/kg bw/day)	Reference
Rat	(assumed to be) single dose, oral	Various, depending on the OP	AChE activity in brain	-20 %	167	(EPA, 2001)

For the remaining 15 OPs no dose-response data were available. Estimates of the RPFs for these OPs were derived from a reference point on the dose-response curve as reported in the JMPR monographs, under the assumption that their dose-response curves are parallel (on log-dose scale) to those for which we do have dose-response data. For the purpose of comparison the CEDs corresponding to 20 % inhibition are estimated for these OPs Table 8 (Bosgra et al., in press).

Table 8. Estimates of the CED corresponding to a 20 % decrease in AChE activity of 30 OPs found in food samples from the Dutch market and RPFs with MMP as index OP.

OP	CED (mg/kg bw)	RPF (MMP as index)
Acephate* (ACP)	4.41	0.036
Azinphos-methyl*	0.48	0.33
Bromophos-ethyl	(6.44)	0.025
Chlorfenvinphos	(0.53)	0.30
Chlorpyrifos*	2.58	0.062
Chlorpyrifos-methyl*	16.6	0.0096
Diazinon*	5.15	0.031
Dichlorvos*	4.65	0.034
Dimethoate*	1.26	0.13
Ethion	(0.15)	1.07
Fenitrothion	(1.54)	0.10
Fenthion*	0.51	0.31
Heptenophos	(1.07)	0.15
Mecarbam	(0.45)	0.36
Methamidophos* (MMP)	0.16	1
Methidathion*	1.03	0.16
Mevinphos*	0.17	0.93
Monocrotophos	(0.031)	5.17
Omethoate	(0.11)	1.50
Parathion	0.86)	0.19
Parathion-methyl*	0.82	0.20
Phosalone*	5.95	0.027
Phosmet*	2.28	0.070
Pirimiphos-ethyl	(0.17)	0.93
Pirimiphos-methyl*	3.57	0.045
Profenphos	(42.9)	0.0037
Pyrazophos	(4)	0.045
Quinalphos	(6.44)	0.025
Tolclofos-methyl	(1494)	0.00011
Triazophos	(28)	0.0057

For OPs marked with an asterix dose-response data were available. For the remaining OPs, JMPR monographs (2008) were used to estimate the RPF. The estimated CEDs of these OPs are shown within brackets.

Extrapolation factor(s)

The CED distribution for AChE activity related to the index chemical is extrapolated to the human situation using an interspecies and intraspecies extrapolation factor. It is assumed that the RPFs as

estimated in the rat are equal in humans (relative to the human CED of the index chemical). Default rat and human body weight are used to derive the allometric factor according to equation (1) (Table 9). In Table 10 an overview is given of the EF distributions used to extrapolate the point of departure to the human target population. Integration of the CED and EF distributions in the probabilistic risk assessment is described in chapter 5.

Table 9. Body weight of the tested and target populations.

Effect	Tested population			Target human population		
	Species	Sex	Mean bw	Age (yr)	Sex	Mean bw
AChE	Rat-7wk	F	0.3	16	F	70

Table 10. EF distributions (all lognormally distributed)

Effects	Allometric fact	Interspecies TK & TD	P95 of intraspecies factor is between:	Intraspecies
AChE	GM=5.1 GSD=1.2	GM=1 GSD=2	2-10	GM=1 GSD=1.9 df=6.25

2.4 Effect characterization T-2/HT-2

Benchmark dose(s)

The immunotoxicity data in the studies from Rafai and Meissonnier were used to perform the probabilistic risk assessment. It should be noted that other studies (Faifer et al., 1992; Hayes et al., 1980; Ohtsubo and Saito, 1977; Rousseaux et al., 1986; Rukmini et al., 1980; Schiefer et al., 1987; Schoental et al., 1979; Sirkka et al., 1992; Smith et al., 1994; Ueno, 1984; Velazco et al., 1996) were examined on useful toxicity data. However, these studies did not provide data in enough detail for effect characterization.

Figures 10 and 11 show the dose response curves of the data from Rafai and Meissonnier, respectively. Figure 11 shows that the highest dose of T-2/HT-2 results in an increased IgA concentration already after one day, an acute effect that remains over time without increasing in strength.

Table 11 shows the summary of the studies used to characterize the dose-response relationships for the toxic effects of T-2/HT-2.

Table 11. Summary of the studies used to characterize the dose-response relationships for the effects of T-2/HT-2.

Species	Exposure	Doses (mg/kg bw/d) (N per group)	Effects considered for dose-response analysis	CES	CED (mg/kg bw/d)	Reference
Pig	21 days in feed	0, 0.029, 0.062, 0.105, 0.129 (10)	White blood cell count	-5 %	0.02	(Rafai et al., 1995)
			Lymphocyte stimulation test (dy 7)	-5 %	10.1	
			Phagocytic index	-5 %	0.06	
Pig (male)	28 days in feed	0, 0.03, 0.07, 0.12 (5)	Plasma IgA concentration	+5 %	0.06	(Meissonnier et al., 2008)

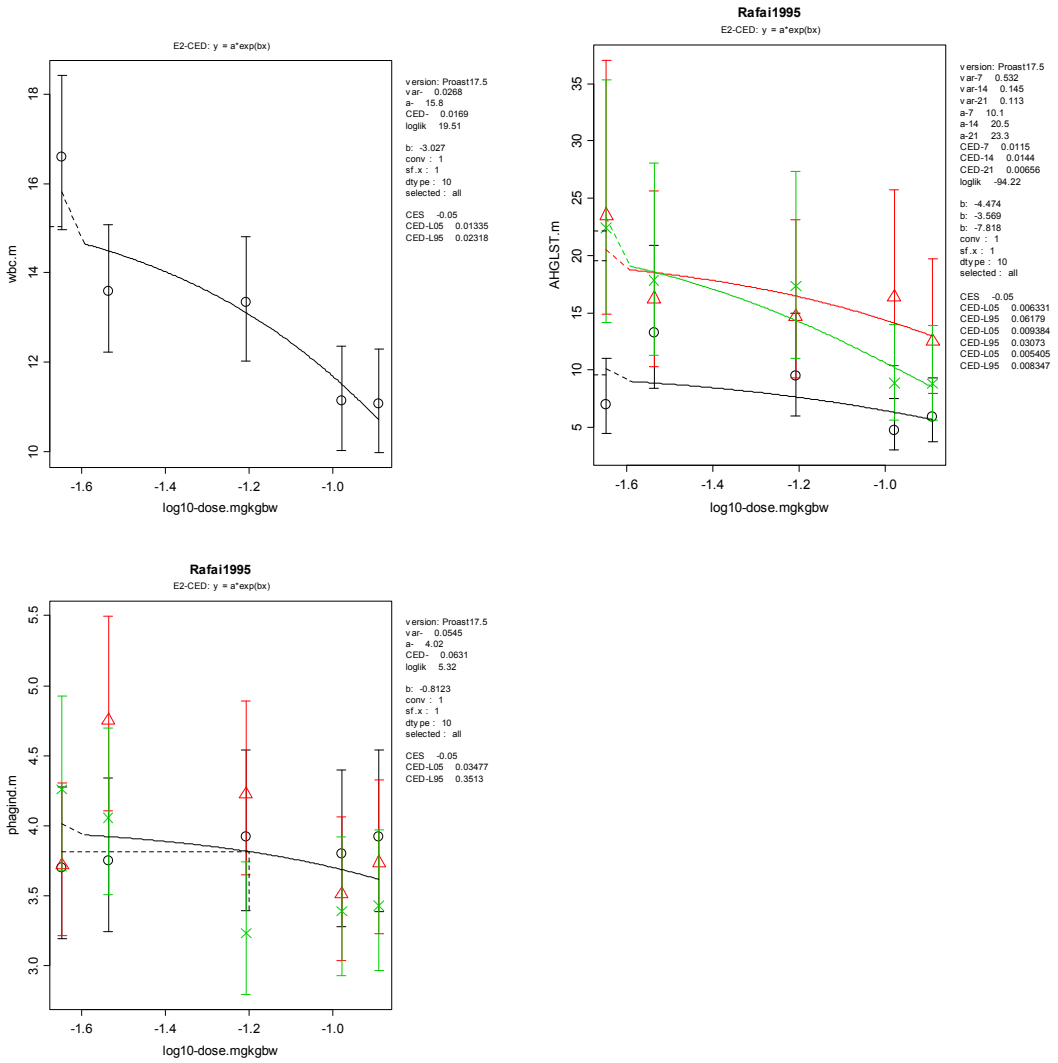


Figure 10. Dose-responses of white blood cell count (WBC), lymphocyte stimulation (AHGLST), and phagocytic index (PI) against $\log_{10}$ of dose (mg/kg bw/d). The latter two endpoints were measured three times during the study; at day 7 (circles), 14 (triangles), and 21 (crosses). The curve for the phagocytic index is the same at each measuring time.

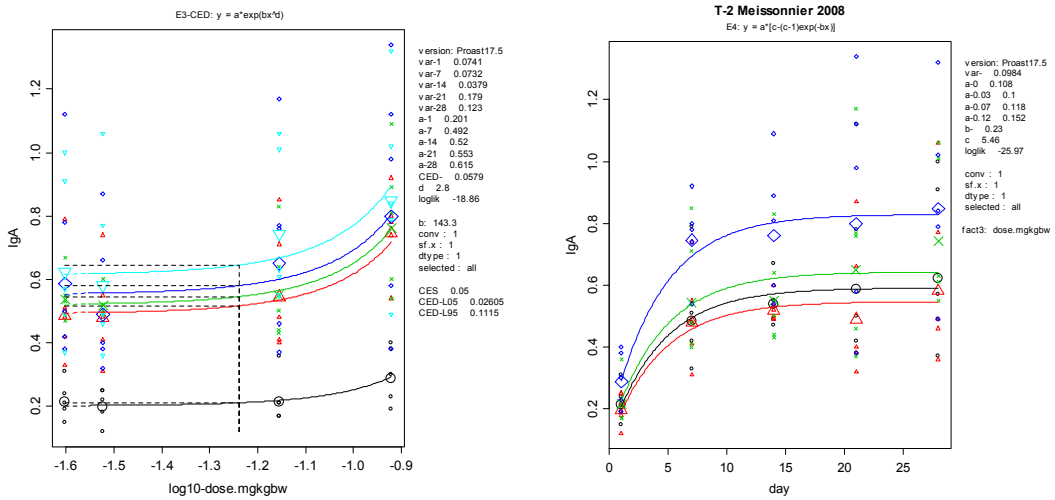


Figure 11. Left: Plot of plasma IgA concentration against $\log_{10}$ dose (mg/kg bw/d). IgA was measured five times during the study; at day 1 (O), 7 (Δ), 14 (×), 21 (◊), and 28 (∇).
Right: Same data, with day of measurement on the x-axis, and dose as the covariate, with dose (mg/kg bw/d) levels: 0 (O), 0.03 (Δ), 0.07 (×), and 0.12 (◊)
In the left panel, parameter *b* is not significantly different among observation times (log-likelihood ratio test; see Slob, 2002), which indicates that the strength of the dose-response does not increase over time (i.e., dose-response curves are parallel on log-IgA scale).

Extrapolation factor(s)
The animal-derived CED distributions are extrapolated to the human situation using an interspecies and intraspecies extrapolation factor.
In Table 12 the animal and human body weights are shown that are used to derive the allometric factor (according to equation (1)). When available, the animal body weights are derived from the study reports, otherwise default body weights were applied. The body weights of the target populations are obtained from DNFCS-3.
In Table 13 an overview is given of the EF distributions used to extrapolate each effect to the human situation.
Integration of the CED and (other) EF distributions in the probabilistic risk assessment will be described in chapter 5.

Table 12. Body weight of the tested and target populations.

Effect	Tested population			Target human population		
	Species	Age	Mean bw (kg)	Age	Sex	Mean bw
White blood cell count Lymphocyte stimulation test Phagocytic index	pig	1-2 months	18.4	1-4	Not specified	14.5
Plasma IgA concentration	pig	1-2 months	30	1-4	M	14.5

Table 13: EF distributions (all lognormally distributed).

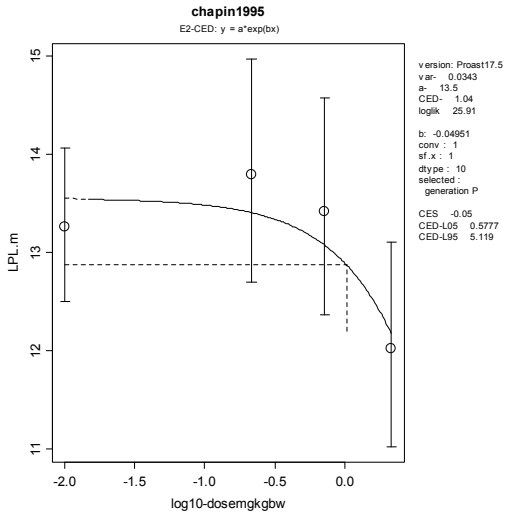
Effect	Allometric factor	Interspecies TK & TD	P95 of intraspecies factor is between:	Intraspecies
White blood cell count Lymphocyte stimulation test Phagocytic index	GM=0.93, GSD=1.0	GM=1.0, GSD=2.0	2-10	GM=1.0 GSD=1.9 df=6.25
Plasma IgA concentration	GM=0.8, GSD=1.0	GM=1.0, GSD=2.0	2-10	GM=1.0 GSD=1.9 df=6.25

2.5 Effect characterization acrylamide

Benchmark dose(s)

A literature review was performed to identify toxicity studies with acrylamide. The relevant effects induced by acrylamide included neurotoxicity as measured by grip strength. Data on carcinogenicity were not obtained since the current probabilistic approach was not developed for assessing carcinogenicity (see Discussion). Other endpoints that showed dose-related effects were the number of life pups/litter and body weight gain. The quantal effect 'life pups/litter' was analyzed as continuous data since the appropriate data to express the life pups/litter in a fraction of the total number of implantation sites were not available. The dose-response data of these endpoints are shown in Figure 12. Table 14 summarizes the relevant endpoints and the key studies. Furthermore, the CES and the best estimate CED are listed for each endpoint.

A)



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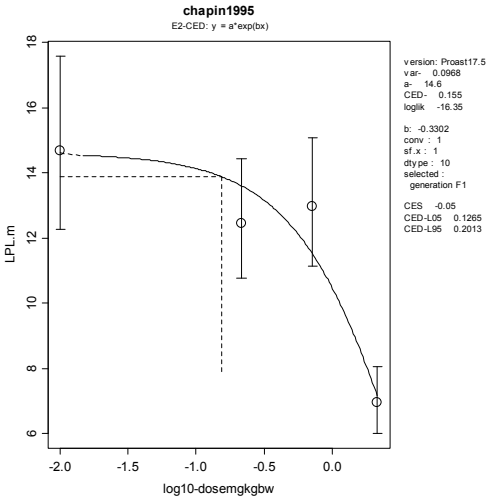
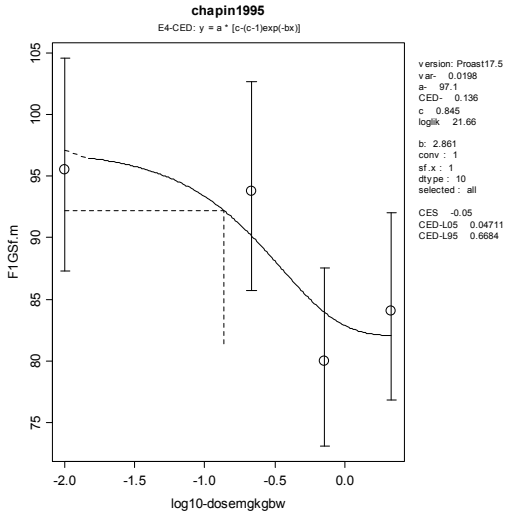


C)



D)

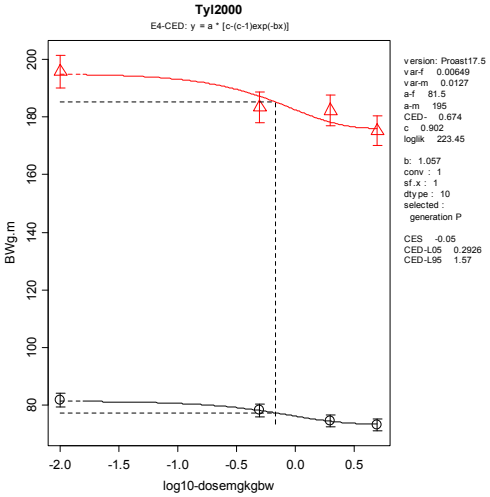


Figure 12. Dose-responses of A) life pups per litter of the P generation, B) life pups per litter of the F1 generation, C) forelimb grip strength of the F1 generation, and D) body weight gain of the P generation (triangles: males, circles: females).

Table 14. Summary of the studies used to characterize the dose-response relationships for the effects of acrylamide.

Species	Exposure	Doses (mg/kg bw) (N per Group)	Effect considered for dose-response analysis	CES	CED (mg/kg bw)	Reference
Mouse	2-generations, drinking water	0, 3, 10, 20 ppm (40, 20,	F1 live pups/litter	-5 %	0.16	(Chapin et al., 1995)
Mouse		20, 20/sex)	F1 grip strength forelimb	-5 %	0.14	
Mouse			P live pups /litter	-5 %	1.04	
Rat	2-generations, drinking water	0, 0.5, 2.0, 5.0 mg/kg bw/d (30/sex)	P BW gain	-5 %	0.67	(Tyl et al., 2000)

Extrapolation factor(s)

The animal derived CED distributions are extrapolated to the human situation using an interspecies and intraspecies extrapolation factor.

In Table 15 the animal and human body weights are shown that are used to derive the allometric factor (according to equation (1)). When available, the animal body weights are derived from the study reports, otherwise default body weights were applied. The body weights of the target populations are obtained from DNFCS-3.

In Table 16 an overview is given of the EF distributions used to extrapolate each effect to the human situation.

Integration of the CED and EF distributions in the probabilistic risk assessment will be described in Chapter 5.

Table 15. Body weight of the tested and target populations.

Effect	Tested population			Target human population		
	Species	Sex	Mean bw	Age	Sex	Mean bw
F1 live pups/litter	mouse	F	0.03	15-45	F	67.3
F1 grip	mouse	M	0.03	all	M	63
strength	mouse	F	0.03	all	F	57.8
forelimb						
P live pups/litter	mouse	F	0.03	15-45	F	67.3
P BW gain	rat	M	0.25	1-19	M	34.1

Table 16. EF distributions (all lognormally distributed).

Effect	Allometric factor	Interspecies TK & TD	P95 of intraspecies factor is in the range:	Intraspecies
F1 live pups/litter	GM=10.1 GSD=1.3	GM=1.0, GSD=2.0	2-10	GM=1.0 GSD=1.9 df=6.25
F1 grip strength forelimb				
M	GM=9.9 GSD=1.3	GM=1.0, GSD=2.0	2-10	GM=1.0 GSD=1.9
F	GM=9.7 GSD=1.3			df=6.25
P live pups /litter	GM=10.1 GSD=1.3			
P BW gain				
M	GM=4.4 GSD=1.2	GM=1.0, GSD=2.0	2-10	GM=1.0 GSD=1.9
F	GM=5.0 GSD=1.2			df=6.25

3 Exposure characterization

Consumption data
For the exposure assessments food consumption data from the Dutch National Food Consumption Survey of 1997/1998 (DNFCS-3) were used (Kistemaker et al., 1998; Voedingscentrum, 1998).

Subpopulations
Based on the toxicological effects a (sub)population may contain one or both sexes and a particular age range (see chapter 2). For example, when an effect occurs in female rats of reproductive age then the mean body weight of women of reproductive age should be used for allometric scaling. When the toxicity studies indicate acute effects and no particular age groups at risk then the whole population (age 1-97, both sexes) can be used or the choice of an age range can be based on knowledge or hypotheses about the exposure. For example, the exposure to OPs and T-2/HT-2 is assumed relatively high at young age when the exposure is expressed per kg body weight. Therefore, and because acute effects are considered for these compounds, children within a particular age range are assumed to be relevant age groups.

Concentration data
The concentration data of various years for DON (2002-2006), cadmium (1999-2006), OPs (2005-2006), and acrylamide (2006-2007) were derived from monitoring programs performed in the Netherlands by the Dutch Food and Consumer Product Safety Authority (VWA). Pesticide residue data was also derived from monitoring programs performed by the Dutch Produce Association (e.g. The Greenery), Bakker Barendrecht B.V. (retail) and Food Compass. The concentration data of T-2/HT-2 was obtained from literature (see section 3.4).
Because the compounds (except acrylamide) are partly analyzed in raw agricultural commodities (RACs), the Conversion model Primary Agricultural Products (Van Dooren et al., 1995) was used to translate the consumption of foods into the consumption of RACs. In this way the concentrations analyzed in RACs could be linked directly to consumption. Concentrations measured in foods were directly linked to consumption levels of the relevant foods.

Samples with levels below the limit of reporting
Food samples are reported to contain a compound at a certain, quantifiable level. However many samples are reported to contain no compound below a certain level(the so-called non-detects). This level is termed the limit of reporting (LOR). For most of the basic exposure analyses (best estimate) non-detects were assumed to contain concentrations equal to 0.5•LOR. Assigning either zero or LOR was considered to result in either an under- or overestimation of exposure, respectively. Whether to assign 0.5•LOR to analyzed foods or RACs with only non-detect levels was determined by the possibility that the food or RAC could be contaminated. For pesticides non-detects were assumed to contain no pesticide residue. Because only a certain part of the commodities will be treated with pesticides, a large part of the non-detects will really not contain the pesticide. Therefore non-detects are commonly assumed to be true zeros.

Processing factors
For DON and the OPs processing factors were included in the exposure calculations. Processing factors are relevant when analyses are performed in RACs which undergo a certain form of processing before consumption, like peeling, cooking, washing, juicing, etc. Processing is known to affect the concentration of a compound (mainly reduction). Ignoring the effect of processing may often result in

an overestimation of the exposure, but may at (rare) times underestimate the concentrations of a compound present in foods as consumed (e.g. increase of mycotoxins during storage). For a detailed description of the applied processing factors see Boon et al. (in prep.).

Exposure assessment
The exposure was derived using Monte Carlo Risk Assessment program (MCRA), version 6.0 (De Boer and Van der Voet, 2007).

Depending on the expected (unknown) actual exposure and the corresponding effect(s) chronic, acute, or both exposures are derived. In an acute exposure assessment the whole range of analyzed concentrations is used to take the variation in concentrations into account. In chronic exposure assessments the mean concentration of the substances in the various foods is used, because this is considered the best representation of the concentration to which an individual will be exposed on the long run.

Acute exposure
For the estimation of the acute exposure 100,000 randomly drawn daily consumption patterns of RACs were multiplied with randomly selected compound specific concentrations per RAC. Summing over RACs resulted in an empirical estimate of the acute exposure distribution. This distribution is assumed to describe the varying exposure between individuals, i.e. the IEXP, which is needed in the integrated probabilistic risk assessment (see chapter 4).

Chronic exposure
A distribution of exposure, calculated as described above using mean concentrations per food or food group, includes both the variation between individuals and between the two recorded days of one individual. However, to assess the long-term exposure within a population only the former type of variation is of interest, since on the long run the variation between different days of one individual will cancel out. Therefore, to calculate a long-term distribution, the within-person (between days) variation should first be removed from the data using statistical modeling. Here the beta-binomial-normal model (BBN, De Boer et al., in prep.; Slob, 2006a) is applied to estimate the chronic exposure of the relevant subpopulation without age as a covariable. To remove the within-person variation from the data, the BBN model transforms the short-term exposure distribution into a normal distribution. After removal of the within-person variation, the normal distribution is back-transformed and is now considered a long-term exposure distribution. This distribution is assumed to describe the varying exposure between individuals, i.e. the IEXP, which is needed in the integrated probabilistic risk assessment (see chapter 4).

3.1 Exposure characterization DON

The exposure assessment of DON was conducted using the same concentration data, processing factors and decisions on how to handle concentration data below LOR as described in a recent previous exposure assessment of DON (Boon et al., in prep.).

The dietary exposure for different subpopulation groups was calculated depending on the effect considered (section 2.1). For the effects on body weight, a chronic exposure assessment was performed in boys and girls in the age range where growth occurs (age 1 to 19). For effects on fertility, a chronic exposure assessment was performed in men at reproductive age (age 15 to 45). For effects on

developmental toxicity, an acute exposure characterization is performed for women at reproductive age (age 15 to 45). Acute exposure is considered because it is assumed that there is a (short-term) critical window during gestation for these effects. An overview of the exposure of each subpopulation is given in Table 17, where the median (50th percentile, P50) and a high percentile (95th percentile, P95) of the exposure distributions are reported.

Table 17. Summary of the acute or chronic DON intakes of the relevant (sub)populations.

Effect	Acute/Chronic	Age	Sex	Percentiles of exposure (µg/kg bw/d)	
				P50	P95
All male fertility effects	C	15-45	M	0.20	0.84
All developmental effects	A	15-45	F	0.03	0.39
Body weight	C	1-19	M & F	0.15	0.44

3.2 Exposure characterization cadmium

The dietary exposure of cadmium was derived depending on the effect considered. Bone mineral density, kidney dysfunction and osteoporosis are considered effects that occur after life-long exposure to cadmium (section 2.2). For the effect on bone mineral density, a chronic exposure assessment is performed in girls in the age range of 15 to 20. This is considered a comparable age range to the range at which a decrease in bone marrow density occurs in the rat study. For kidney dysfunction and osteoporosis a chronic exposure assessment is performed in adults (age 20 to 70).
An overview of the exposure of each relevant subpopulation is given in Table 18, where the P50 and P95 of the exposure distributions are reported.

Table 18. Summary of the chronic cadmium intakes of the relevant (sub)populations.

Effect	Acute/Chronic	Age	Sex	Percentiles of exposure (µg/kg bw/d)	
				P50	P95
Bone mineral density	C	15-20	F	0.17	0.24
Osteoporosis	C	20-70	M & F	0.15	0.25
Kidney dysfunction	C	20-70	M & F	0.15	0.25

3.3 Exposure characterization OPs

It has been suggested that children may be a specific risk group due to higher intake of OPs per kg body weight (Boon et al., 2008). Therefore, we focused on children between 1 and 6 years of age. Since the decrease in AChE activity due to exposure to OPs is instantaneous an acute exposure

assessment is performed for this effect and subpopulation. To derive the cumulative exposure of the various OPs additional calculations are needed, which are described below.

Cumulative acute exposure
Modeling of the cumulative acute exposure is performed using the RPF (Relative Potency Factor) method (Boon et al., 2008; Bosgra et al., in press). There are no international guidelines on how to perform these calculations. Here, the cumulative exposure to OPs is estimated by linking daily consumption levels of raw agricultural commodities (RACs) with summed OP concentrations per relevant RAC sample expressed in methamidophos (MMP) equivalents. This is done by multiplying the concentration (mg OP/kg RAC) of each OP in a sample by its RPF (Table 8) and adding up the different equivalents to one OP concentration per RAC expressed in MMP-equivalents. Subsequently, these samples are used in a regular acute exposure characterization.
An overview of the exposure of the subpopulation is given in Table 19, where the P50 and P95 of the exposure distribution are reported.

Table 19. Summary of the acute intake of OPs of the relevant (sub)population.

Effect	Acute/Chronic	Age	Sex	Percentiles of exposure (ng/kg bw/d)	
				P50	P95
AChE activity	A	1-6	F	6.34	82.2

3.4 Exposure characterization T-2/HT-2

In contrast to the other compounds described in this report the concentration data on T-2/HT-2 in foods in the Netherlands are scarce. Therefore, concentration data were obtained from public literature (Cervero et al., 2007; Muller et al., 1997; Rasmussen et al., 2003; Schollenberger et al., 2002; 2008; 2005; Scoop, 2003). A disadvantage of these data is that they are not reported in the required detail. Some assumptions are needed to circumvent the lack of detail.

T-2/HT-2 causes immediate immunotoxic effects (e.g. Figure 11), which requires an acute exposure characterization. To derive the acute exposure distribution, individual concentrations are needed. However, the mean or median concentrations, sample sizes, and number of non-detects were reported, but a measure of the variance was not (or seldomly) given. To overcome this, the standard deviation of the DON concentration was used as measure of variance, because DON and T-2 are produced by the same family of fungi (trichothecenes). When the concentrations of DON and T-2 are considered dependent on the amount of fungi on a product, then the variance in DON concentrations might be similar to that of T-2. Knowledge on the variance in addition to the mean or median enables the estimation of the exposure distribution.
Another problem is that the T-2 and HT-2 concentrations are reported separately. Since T-2 and HT-2 are assumed to elicit the same effect, by the same mode of action, the cumulative exposure of the two compounds should be derived. This requires the summed concentrations of T-2 and HT-2 for each food (product), which information is not available. Individual concentrations were therefore derived by random sampling from the T-2 and HT-2 distributions, taking into account both the standard deviation

of DON as measure of variance and the ratio of detects/non-detects. Individual concentrations of T-2 and HT-2 are summed taking into account the correlation of co-occurrence on a product as reported by Langseth and Rundberget (1999). They report a correlation of 0.73 for the co-occurrence of T-2 and HT-2 toxin.

The dietary exposure for different subpopulation groups was calculated depending on the effect considered (section 2.4). For the immunotoxic effects, an acute exposure assessment was performed in boys and girls age 1 to 4. The exposure is assumed relatively high at young age when the exposure is expressed per kg body weight (Boon et al., 2008).
An overview of the exposure of the subpopulation is given in Table 20, where the P50 P95 of the exposure distribution are reported.

Table 20. Summary of the acute T-2/HT-2 intakes of the relevant (sub)populations.

Effect	Acute/Chronic	Age	Sex	Percentile of exposure (µg/kg bw/d)	
				P50	P95
White blood cell count	A	1-4	M&F	0.11	0.54
Lymphocyte stimulation test	A	1-4	M&F	0.11	0.54
Phagocytic index	A	1-4	M&F	0.11	0.54
Plasma IgA concentration	A	1-4	M&F	0.11	0.54

3.5 Exposure characterization acrylamide

The dietary exposure to acrylamide was derived for different subpopulation groups depending on the effect considered (section 3.5).

For effects on fertility (in generation P and F1), an acute exposure assessment is performed for women at reproductive age (age 15 to 45). Acute exposure is considered because it is assumed that there is a (short-term) critical window during gestation for pup death. For grip strength a chronic exposure assessment is performed in males and females (generation P) of all ages present in DNFCS-3. All ages are included since this effect is assumed to occur after repeated exposure and no specific sensitive subpopulation is assumed present. For the effects on body weight gain, a chronic exposure assessment is performed in males and females (generation P) in the age range where growth occurs (age 1 to 19). Analysis of the exposure data indicated that men and women have significant different exposures (when expressed per kg body weight). Therefore the exposures for both sexes are reported separately for body weight gain.

An overview of exposure of each subpopulation is given in Table 17, where the P50 and P95 of the exposure distributions are reported.

Table 21. Summary of the acute or chronic acrylamide intakes of the relevant (sub)populations.

Effect	Acute / Chronic	Age	Sex	Percentiles of exposure (ng/kg bw/d)	
				P50	P95
P Live pups /litter	A	15-45	F	0.22	1.3
F1 live pups/litter	A	15-45	F	0.22	1.3
F1 Grip strength	C	1-97	M	0.33	0.80
forelimb	C	1-97	F	0.32	0.73
P BW gain	C	1-19	M	0.47	1.3
	C	1-19	F	0.41	1.0

4 Integrated probabilistic risk assessment

In the present approach (Van der Voet and Slob, 2007) the probabilistic data described in the previous chapters are integrated to perform a risk assessment. In short the procedure is as follows: it is assumed that each individual has his/her own susceptibility level, i.e. some dose (or exposure) that will result in a particular effect. This dose is termed ICED. The ICED is derived by dividing the experimentally obtained CED by one or various EFs. Furthermore, it is assumed that the exposure varies between individuals: they all have their own individual exposure (IEXP). The ratio of ICED and IEXP is termed the individual margin of exposure:

$$IMoE = \frac{ICED}{IEXP} \qquad (2)$$

The IMoE indicates whether the exposure of a particular (but unknown) individual exceeds his/her personal dose at which a defined effect will occur. When the IMoE is below 1 the effect will occur, and above 1 it will not occur. Note that the IMoE should be interpreted in a different way compared to the (classical and deterministic) margin of exposure (MoE)[2].

The ICED and IEXP (and thus the IMoE) are unknown for any specific individual. However, it can be estimated which IMoEs may occur in the population with what frequency. This is done by Monte Carlo simulation: a large number of individuals are simulated to whom random values are assigned for all parameters that vary between individuals. These values are randomly drawn from datasets or specified variability distributions. The risk can be summarized by a characteristic of the IMoE distribution, such as a fraction of the population with an IMoE below 1, or a particular percentile of the IMoE distribution.

The uncertainty associated with each of the parameters in the assessment is evaluated by an uncertainty analysis: the Monte Carlo simulation is repeated many times, by drawing random values for all specific uncertainty parameters in each run. This sampling procedure results in an uncertainty distribution for a characteristic summarizing the IMoE distribution. The uncertainty is summarized by a confidence interval.
For a detailed description of the integrated probabilistic risk assessment procedure that is applied in this report, see Van der Voet and Slob (2007).

As mentioned above, the risk can be summarized by a characteristic of the IMoE distribution. There are various characteristics that could be presented. Here, the following characteristics for the risk are reported:

- the fraction of the population with an IMoE below 1, indicating the fraction of the population affected[3];
- the fraction of the population with an IMoE below 10, 100, etc.;
- a lower percentile of the IMoE distribution, e.g. of the 1st percentile of the population;
- the range of IMoEs for 98 % of the population (1st to 99th percentile).

[2] MoE is the ratio between the actual exposure and an experimentally derived Point of Departure, such as the CED(L), BMD(L) or NOAEL. The MoE should be larger than the product of the assessment factors, while the IMoE should be larger than one.

[3] Also termed probability of critical exposure (Van der Voet and Slob 2007)

The uncertainty of the selected fraction or percentile is summarized by a two-sided 90 %-confidence interval. Note that the confidence intervals reported by the IPRA software take the well-known and usually considered sources of uncertainty into account, and in that sense they give an adequate impression of the overall uncertainty in the risk estimates.
In the presented case studies the estimated fraction of the population with an IMoE below 1 is always very small. Therefore, in this report the IMoE of a lower percentile of the population and the lower confidence bound thereof are given special interest.

In the IPRA software uncertainty analysis is an integral part of the risk assessment. There are numerous sources of uncertainty in risk assessment and the uncertainties can be substantial. It is neither practical nor necessary to conduct the most detailed uncertainty analysis in every risk assessment. The level of detail in the uncertainty analysis should be in line with the needs of the risk assessment (i.e. what question is addressed?).

In general, an assessment of uncertainties in risk assessment model inputs will reveal two categories of uncertainty:

- quantified uncertainties
- qualified or non-quantified uncertainties

Currently, the IPRA software incorporates the possibility to estimate the contribution of several sources of quantified uncertainty. These sources are the Monte Carlo analysis, consumption data, concentration data, the experimentally derived CED, and the various extrapolation steps. The contribution of these sources to the uncertainty is presented in each case study. It should be noted that the contribution depends on the regarded IMoE and endpoint. Therefore, a fixed level is chosen at which the contributions of the various sources are derived: the 1st percentile of the population.

The non-quantified uncertainties should be described and discussed, for example using the tabular format proposed by EFSA (2006). Preferably, some estimate should be given for the order of magnitude of the non-quantified uncertainties relative to the quantified uncertainties. The present case studies are performed to illustrate the applicability and feasibility of an integrated probabilistic risk assessment. Therefore no elaborate descriptions of the non-quantified uncertainties are given in these case studies. For examples and guidance on methods to describe and discuss the non-quantified uncertainties the reader is referred to EFSA (2006), De Mul et al. (2008), and Van Ooijen et al. (in prep.).

4.1 Integrated probabilistic risk assessment DON

Figure 13 shows the cumulative distribution function of the individual margins of exposure (IMoE) for a 5 % body weight decrease in the population (of 1-19 year old boys and girls) by DON. The higher the values of IMoE, the lower the risk. An IMoE of less than 1 (=1e+00) indicates that the effect, i.e. a body weight decrease larger than 5 %, occurs. The central curve indicates the best estimate for the IMoE cumulative distribution, whereas the two outer curves represent the 90 % confidence interval for this distribution based on the uncertainty analysis. The horizontal lines indicate the best estimate of the population with an IMoE $\leq$ 10 (=1e+01) and $\leq$ 100 (=1e+02). The horizontal line corresponding to IMoE $\leq$ 1 (=1e+00) drops below the plotted area.

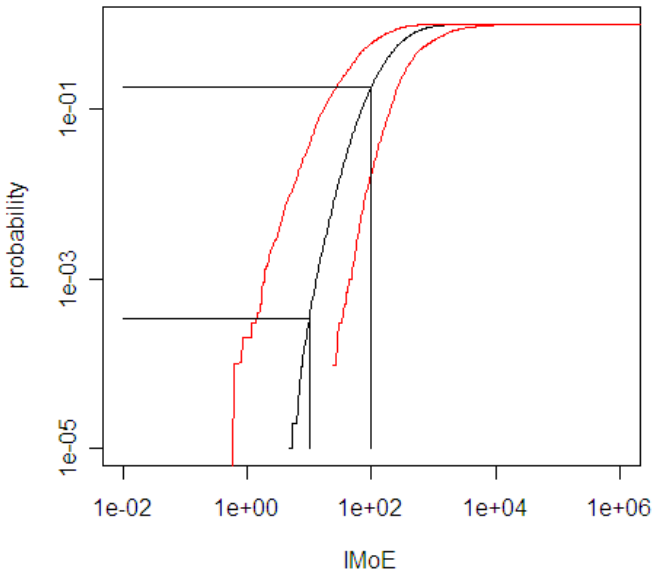


Figure 13. Cumulative distribution of the Individual Margins of Exposure (IMoE) for a 5 % decrease in body weight by DON. The central line indicates the best estimate for the IMoE distribution, whereas the outer lines indicate the 90 % confidence interval for the IMoE distribution.

It can be read from this plot, for instance, that the best estimated percentage of the population with an IMoE of ≤ 1 (=1e+00) is smaller than 0.001 % (probability=1e-05). When looking at the confidence interval in a vertical direction it can be concluded that, with 95 % confidence, a maximum of 0.02 % (probability 2e-04) of the population has an IMoE ≤ 1. When looking at the confidence interval in a horizontal direction one can, for example, conclude with 95 % confidence that 99 % of the population has an IMoE of >5.

In principal, all risk characteristics and uncertainty characteristics can be read from such a plot. However, it is rather difficult to read this graph in sufficient detail. Furthermore, similar graphs are produced for each effect, and the comparison of the results between effects is complicated. In Figure 14 the results are presented in another way, for all DON induced effects. The horizontal bars indicate the IMoE of 98 % of the population (percentile 1 to percentile 99), and the whiskers indicate the 5 % lower bound on the 1st percentile and the 95 % upper bound on the 99th percentile of the population. In this way multiple effects can be compared in a straightforward manner. For the other compounds, cadmium, OPs, T-2/HT-2, and acrylamide, no cumulative distribution plots will be reported, but only the bar plots as in Figure 14.

Figure 14. IMoEs for the effects induced by DON. Bars indicate 98 % of the population (percentile 1 to percentile 99), and whiskers indicate the 5 % lower bound on the 1st percentile and the 95 % upper bound on the 99th percentile of the population. The plot is truncated at an IMoE of one million.

The bars in Figure 14 give some indication of the full range of IMoE values estimated for the target population. However, individuals with a (very) large IMoE (>1000) are simply very safe and therefore the main interest will be on the left hand side. An alternative to displaying the entire distribution is to focus the graphical presentation on the left side of Figure 14. This is presented in Figure 15, where the IMoE of the 1st percentile of the population and its 90 % confidence interval are plotted. The associated summary data are presented in Table 22.

Figure 16 shows, for three effects caused by DON, the relative contribution of a selection of sources of uncertainty to the 1st percentile of the IMoE distribution. The largest contributor to the uncertainty is the interspecies extrapolation factor. It should be noted that the contribution to the uncertainty depends on the endpoint considered.

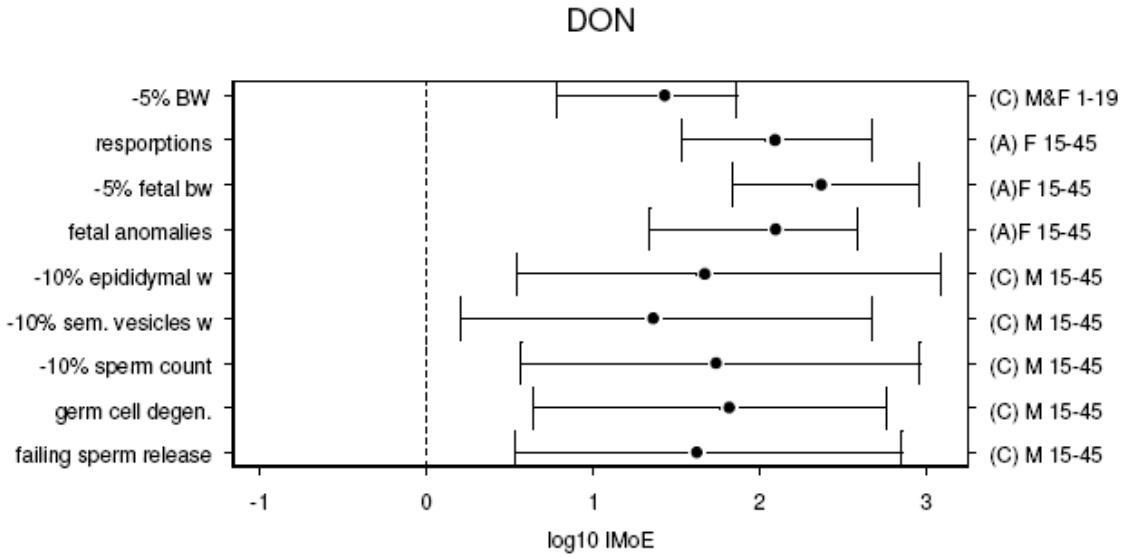


Figure 15. IMoEs for the effects induced by DON. The dots indicate the IMoE of the 1st percentile of the population and whiskers indicate its 5 % lower and 95 % upper confidence limits. On the left y-axis the effect is shown. The right y-axis denotes the exposure duration needed to produce the effect (Acute or Chronic) and the relevant target subpopulation. The vertical dotted line indicates the IMoE of 1.

Table 22. Summary data of the IMoE of the 1st percentile of the population.

Effect	Target population		CES	1st percentile of IMoE distribution		
	Sex	Age		L05[a]	Best estimate	L95[b]
Body weight	M&F	1-19	-5 %	6.0	27	73
Fetal body weight	F	15-45	-5 %	34	124	472
Resorptions	F	15-45	NA[c]	68	236	911
Fetal anomalies	F	15-45	NA[c]	22	125	386
Epididymal w	M	15-45	-10 %	3.5	47	1223
Seminal vesicle w	M	15-45	-10 %	1.6	23	470
Sperm count	M	15-45	-10 %	3.7	55	918
Germ cell degeneration	M	15-45	NA[c]	4.3	66	575
Failure of sperm release	M	15-45	NA[c]	3.4	42	714

[a] L05: 5 % lower confidence limit
[b] L95: 95 % upper confidence limit
[c] no CES is defined because of quantal endpoint

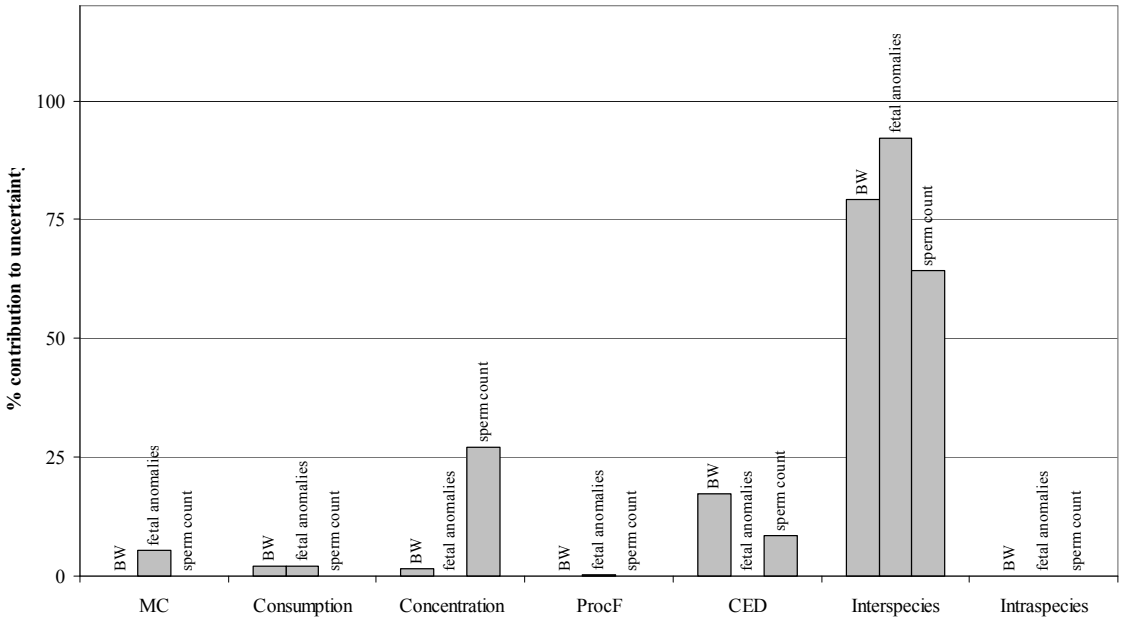


Figure 16. Contribution of various sources of uncertainty to the overall uncertainty in the IMoE at the 1st percentile of the population for a selection of effects caused by DON.

4.2 Integrated probabilistic risk assessment cadmium

In Figures 17 and 18, and Table 23 the results for cadmium induced effects are presented in the same way as in the previous section (4.1) for DON.

Figure 19 shows the relative contribution of a selection of sources of uncertainty in the IMoE of three effects at the 1st percentile of the population. It should be noted that the relative contributions of the various sources to the uncertainty depends on the endpoint.

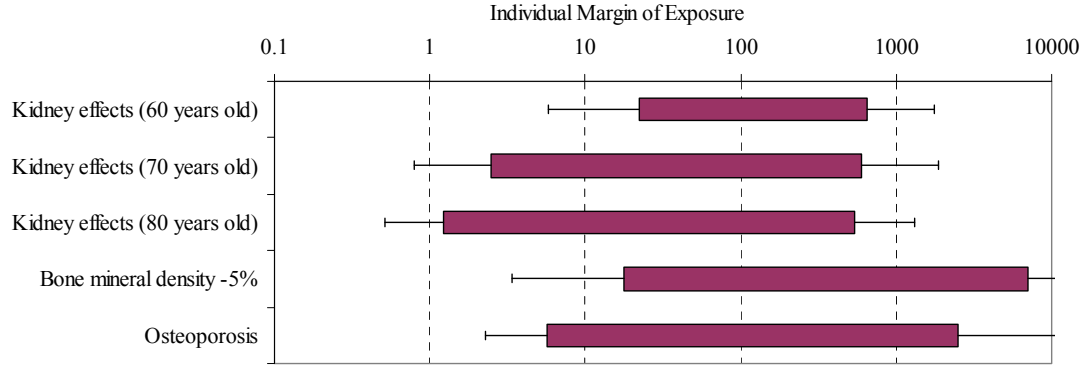


Figure 17. IMoEs for the effects induced by cadmium. Bars indicate 98 % of the population (percentile 1 to percentile 99), and whiskers indicate the 5 % lower bound on the 1st percentile and the 95 % upper bound on 99th percentile. The plot is truncated at an IMoE of one million.

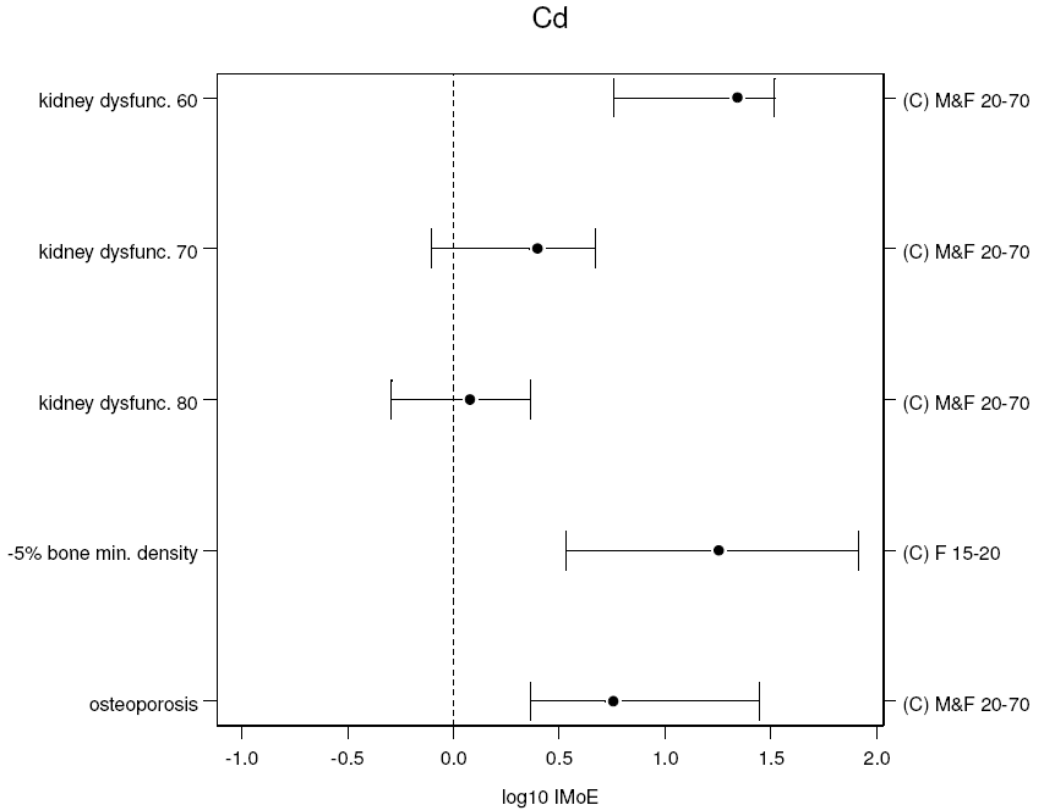


Figure 18. IMoEs for the effects induced by cadmium. The dots indicate the IMoE of 1st percentile of the population and whiskers indicate its 5 % lower and 95 % upper confidence limits. On the left y-axis the effect is shown. The right y-axis denotes the relevant subpopulation and the exposure duration needed to produce the effect (Chronic). The vertical dotted line indicates the IMoE of 1.

Table 23. Summary data of the IMoE of the 1st percentile of the population.

Effects	Target population		CES	1st percentile of IMoE distribution		
	sex	age		L05[a]	Best estimate	L95[b]
Kidney dysfunct. 60	M&F	20-70	1000 µg β2-MG/g creatinine	5.7	22	33
Kidney dysfunct. 70	M&F	20-70	ditto	0.79	2.5	4.7
Kidney dysfunct. 80	M&F	20-70	ditto	0.51	1.2	2.3
Bone mineral density	F	15-20	-5 %	3.4	18	82
Osteoporosis	M&F	20-70	Additional risk: +5 %	2.3	5.7	28

[a] L05: 5 % lower confidence limit
[b] L95: 95 % upper confidence limit

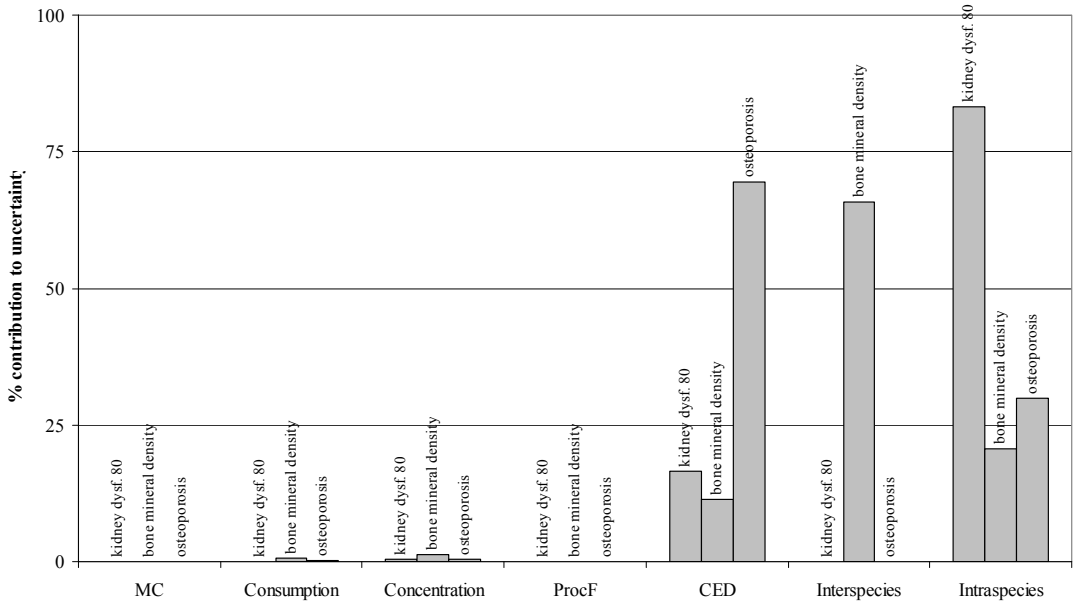


Figure 19. Contribution of various sources of uncertainty to the overall uncertainty in the lMoE at the 1st percentile of the population for the effects of cadmium.

4.3 Integrated probabilistic risk assessment OPs

In Figures 20 and 21, and Table 24 the results for the effect induced by OPs is presented in the same way as in the section (4.1) for DON.

Figure 22 shows the relative contribution of a selection of sources of uncertainty in the IMoE of AChE activity at the 1st percentile of the population. The largest contributor to the uncertainty is the interspecies extrapolation factor. It should be noted that relative contributions of the various sources depends on the endpoint.

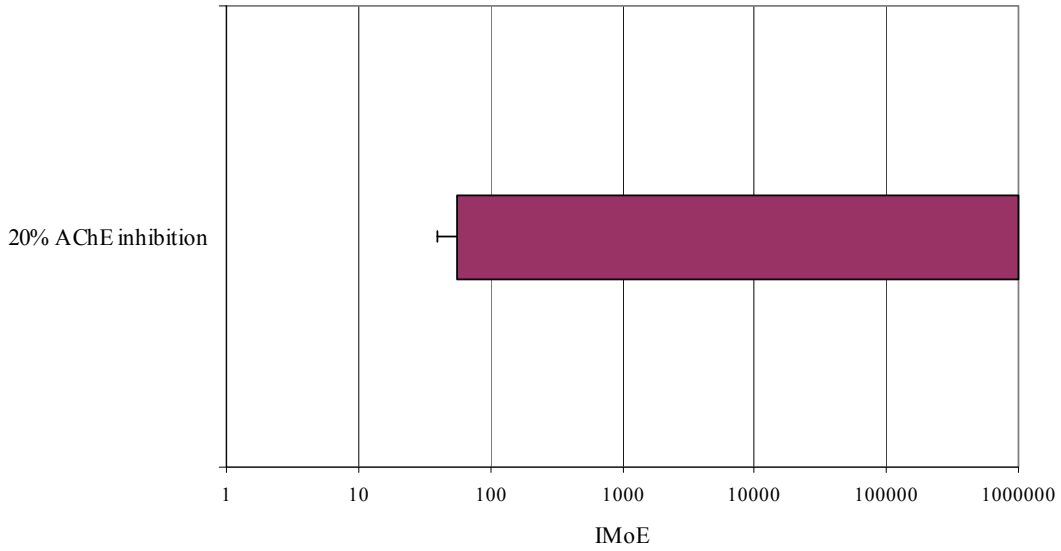


Figure 20. IMoE for the effect induced by OPs. The bar indicates 98 % of the population (percentile 1 to percentile 99), and whiskers indicate the 5 % lower bound on the 1st percentile and the 95 % upper bound on the 99th percentile. The plot is truncated at an IMoE of one million.

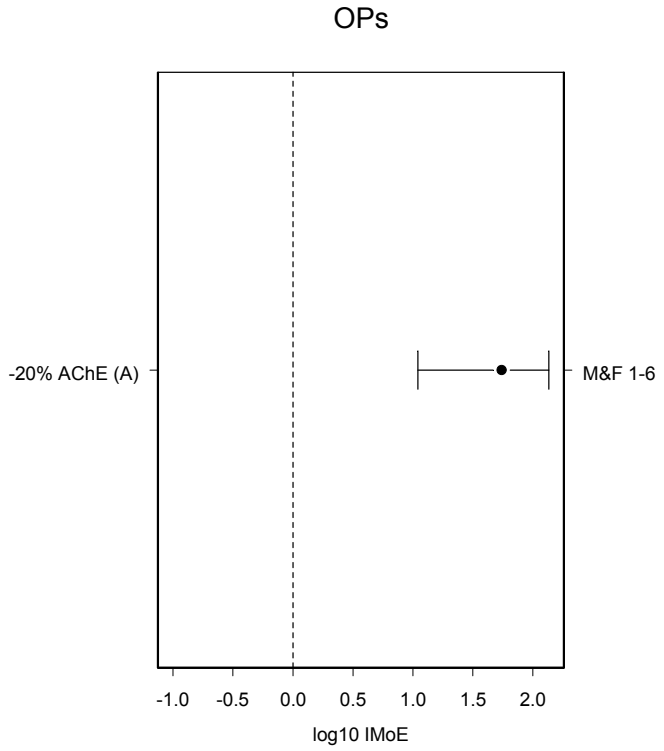


Figure 21. IMoE for the effect induced by OPs. The dot indicates the IMoE of 1st percentile of the population and whiskers indicate its 5 % lower and 95 % upper confidence limits. On the left y-axis the effect and the exposure duration needed to produce the effect (Acute) is plotted. The right y-axis denotes the relevant target subpopulation. The vertical dotted line indicates the IMoE of 1.

Table 24. Summary data of the IMoE of the 1st percentile of the population.

Endpoint	Target population		CES	1st percentile of IMoE distribution		
	sex	age		L05[a]	Best estimate	L95[b]
AChE activity	M&F	1-4	-20 %	11	55	136

[a] L05: 5 % lower confidence limit
[b] L95: 95 % upper confidence limit

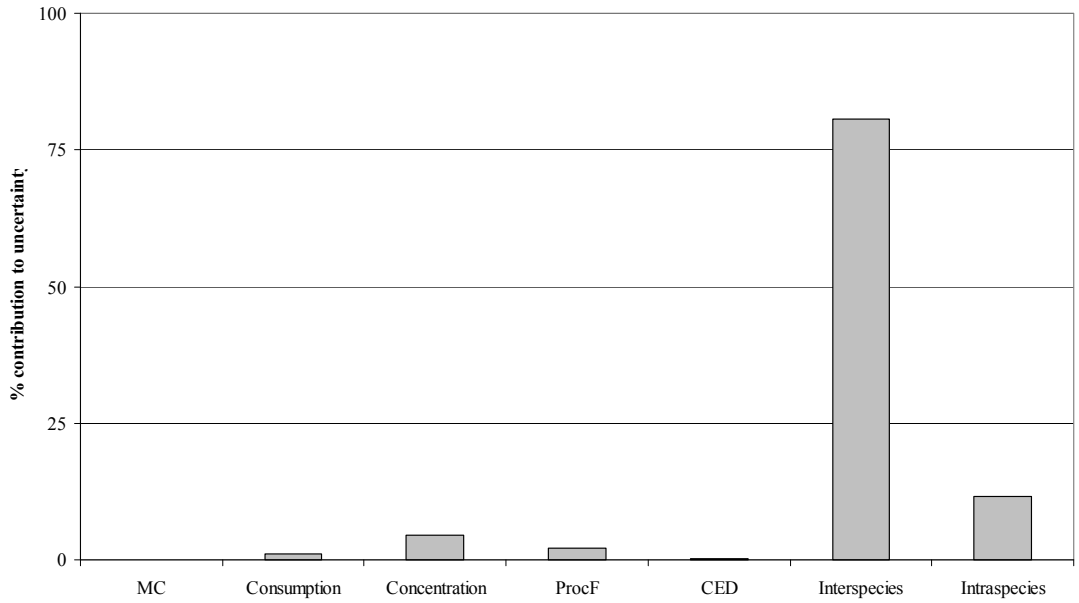


Figure 22. Contribution of various sources of uncertainty to the overall uncertainty in the IMoE at the 1st percentile of the population for AChE effects.

4.4 Integrated probabilistic risk assessment T-2/HT-2

In Figures 23 and 24, and Table 25 the results for T-2/HT-2 induced effects are presented in the same way as in the section (4.1) on DON.

Figure 25 shows the relative contribution of a selection of sources of uncertainty in the IMoE of all endpoints at the 1st percentile of the population. The largest contributor to the uncertainty is the interspecies extrapolation factor. It should be noted that the relative contributions of the various sources depends on the target population.

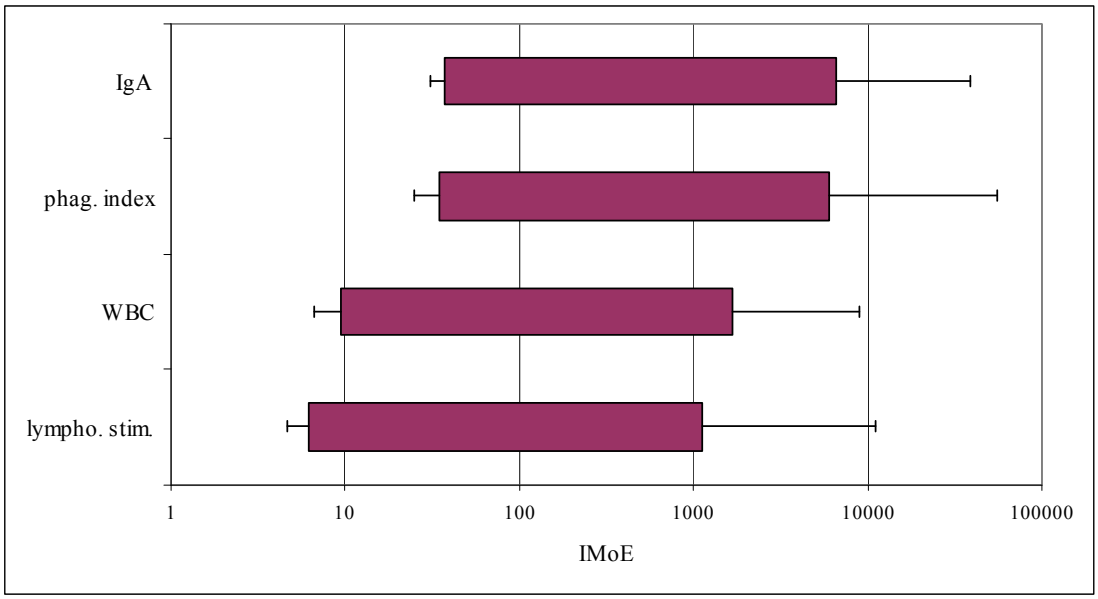


Figure 23. IMoEs for the effects induced by T-2/HT-2. Bars indicate 98 % of the population (percentile 1 to percentile 99), and whiskers indicate the 5 % lower bound on the 1st percentile and the 95 % upper bound on the 99th percentile.

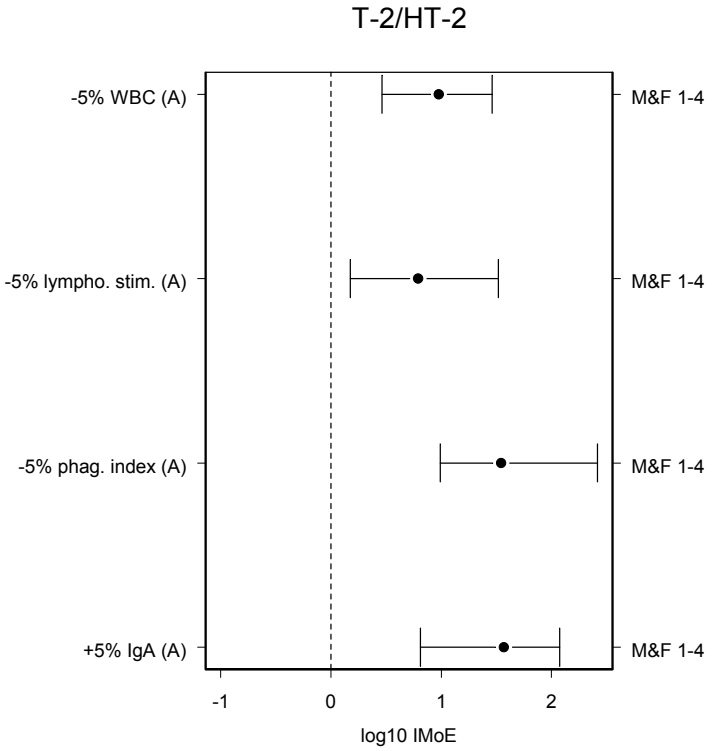


Figure 24. IMoEs for the effects induced by T-2/HT-2. The dots indicate the IMoE of 1st percentile of the population and whiskers indicate its 5 % lower and 95 % upper confidence limits. On the left y-axis the effect and the exposure duration needed to produce the effect (Acute) are plotted. The right y-axis denotes the relevant target subpopulation. The vertical dotted line indicates the IMoE of 1.

Table 25. Summary data of the IMoE of the 1st percentile of the population.

Effect	Target population		CES	1st percentile of IMoE distribution		
	Sex	Age		L05[a]	Best estimate	L95[b]
White blood cell count	M&F 1-4	1-4	-5 %	2.9	9.5	29
Lymphocyte stimulation	M&F 1-4	1-4	-5 %	1.5	6.2	33
Phagocytic index	M&F 1-4	1-4	-5 %	9.8	35	261
Plasma IgA concentration	M&F 1-4	1-4	+5 %	6.5	37	119

[a] L05: 5 % lower confidence limit
[b] L95: 95 % upper confidence limit

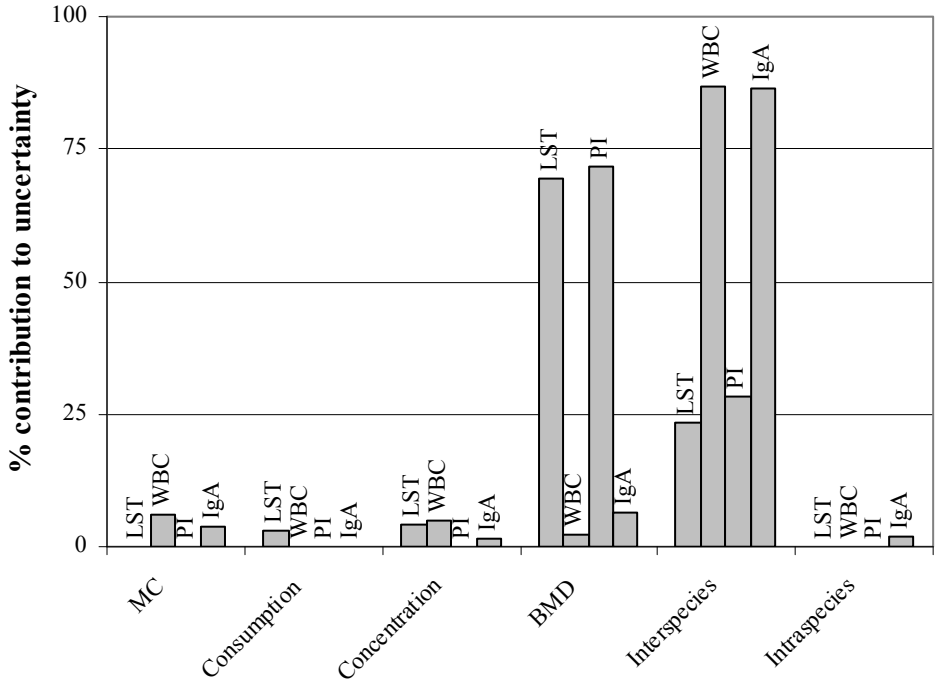


Figure 25. Contribution of various sources of uncertainty (MC= Monte Carlo) to the overall uncertainty in the IMoE at the 1st percentile of the population for each effects: lymphocyte stimulation (LST), white blood cell count (WBC), phagocytic index (PI), and plasma IgA concentration (IgA).

4.5 Integrated probabilistic risk assessment acrylamide

In Figures 26 and 27, and Table 26 the results for acrylamide induced effects are presented in the same way as in the previous section (4.1) on DON.

Figure 28 shows the relative contribution of a selection of sources of uncertainty in the IMoE of all endpoints at the 1st percentile of the population. The largest contributor to the uncertainty is the interspecies extrapolation factor. It should be noted that the relative contributions of the various sources depend on the population percentile considered.

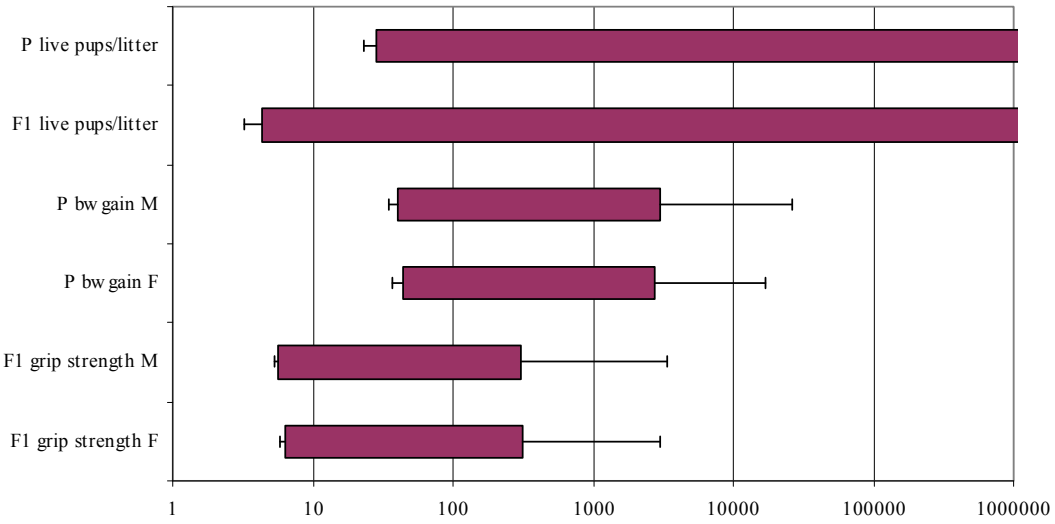


Figure 26. IMoEs for the effects induced by acrylamide. Bars indicate 98 % of the population (percentile 1 to percentile 99), and whiskers indicate the 5 % lower bound on the 1st percentile and the 95 % upper bound on the 99th percentile. The plot is truncated at an IMoE of one million.

Table 26. Summary data of the IMoE of the 1st percentile of the population.

Effect	Target population		CES	1st percentile of IMoE distribution		
	Sex	Age		L05[a]	Best estimation	L95[b]
P live pups/litter	F	15-45	-5 %	5.4	29	177
F1 live pups/litter		15-45	-5 %	1.1	4.3	12
P bw gain	M	1-19	-5 %	5.7	41	172
	F	1-19	-5 %	7.4	44	211
F1 grip strength	M	1-97	-5 %	0.31	5.6	30
	F	1-97	-5 %	0.51	6.3	33

[a] L05: 5 % lower confidence limit

[b] L95: 95 % upper confidence limit

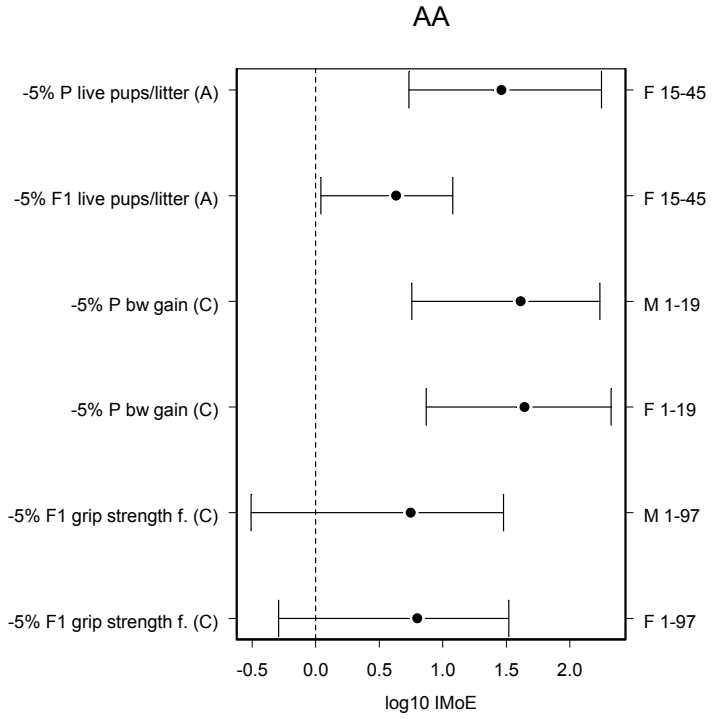


Figure 27. IMoEs for the effects induced by acrylamide. The dots indicate the IMoE of 1st percentile of the population and whiskers indicate its 5 % lower and 95 % upper confidence limits. On the left y-axis the effect and the exposure duration needed to produce the effect (Acute or Chronic) are plotted. The right y-axis denotes the target subpopulation. The vertical dotted line indicates the IMoE of 1.

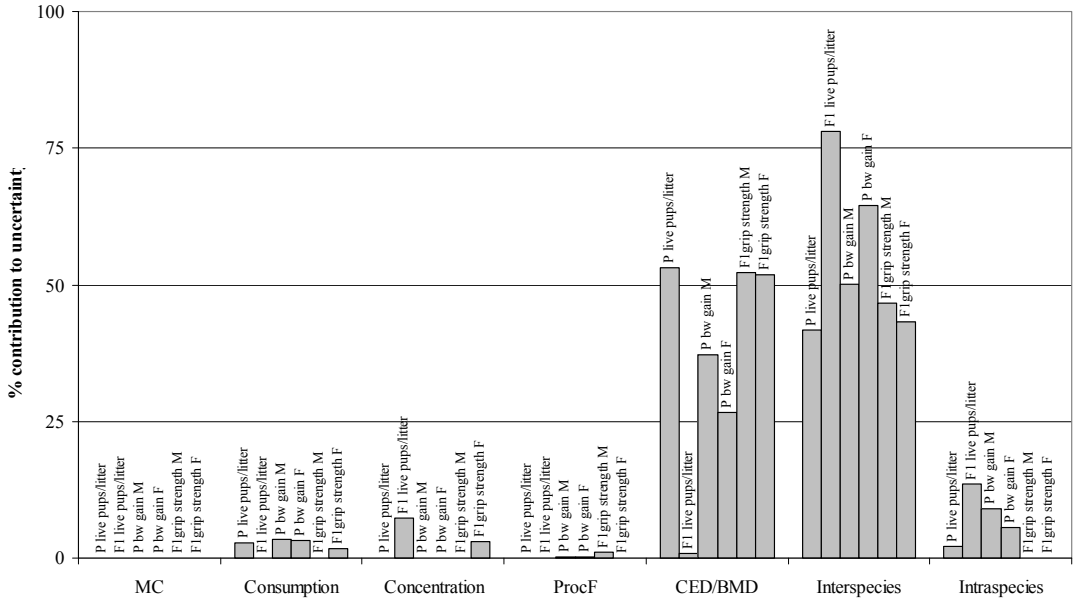


Figure 28. Contribution of various sources of uncertainty (MC= Monte Carlo, ProcF=processing factor) to the overall uncertainty in the IMoE at the 1st percentile of the population for each effects: lymphocyte stimulation (LST), white blood cell count (WBC), phagocytic index (PI), and plasma IgA concentration (IgA).

5 Discussion

Probabilistic risk assessment provides more insight in risks of compounds than the classical deterministic risk assessment approach. The deterministic approach may be suitable as a first tier approach to indicate that even in a worst-case scenario no unacceptable human health risk is expected. However, when risks cannot be excluded a more realistic probabilistic risk assessment may be needed to estimate the actual health impact in the population. The probabilistic approach provides a percentage of a (sub)population that is affected, given a specified effect, together with the uncertainty margins around that estimate.
Below, the various components of a probabilistic risk assessment as proposed by Van der Voet and Slob (2007) are further discussed. The discussion is based on the experiences with the five case study compounds and, focuses on its applicability and feasibility of the integrated probabilistic risk assessment approach.

5.1 Effect characterization

In theory all endpoints which are considered in experimental studies can be analyzed. However, from a practical point of view a limited number of the most sensitive/ relevant endpoints should be selected. Selection of an endpoint depends on several criteria. The main criteria are:

- quality of the study reporting the endpoint
- sufficiently detailed presentation of dose-response data
- consensus among toxicologists about the relevance of the endpoint
- an observed dose-related effect

In general, a well trained toxicologist/risk assessor should be able to make an appropriate selection of the relevant data, as this is also part of the current (deterministic) risk assessment approach.

For some compounds there might be widespread consensus among toxicologists about the critical endpoints of a compound, while the underlying dose-response data are not (publicly) available. In such cases further (quantitative) risk assessment, including an integrated probabilistic risk assessment as presented here, can be performed by using the NOAELs rather then the CED distribution. This would lead to a reduced IPRA, where the uncertainties in the dose-response data cannot be evaluated.

Most of the dose-response data that we were able to retrieve for the five case studies were continuous, and only few were quantal. One of the aims of IPRA is to compare the potential risks associated with the various endpoints. While it is not easy to interpret and compare, say, the risk (fraction of population affected) related to a 5 % change in white blood cells with the risk related a 5 % change in IgA, it is even more difficult to compare a 5 % increase in incidence of osteoporosis with a 5 % decrease in bone density. The comparison of effect sizes in different endpoints is further discussed in Bos et al. (2009).

When the data of a particular endpoint is equally well described by various models then the resulting CED distributions may be combined into one overall CED distribution. This is demonstrated for the DON case. The resulting distribution now includes the uncertainty of the model selection.

After deriving the PoDs from the experimental data EFs are determined to extrapolate the PoDs from the animal to the average human and from the average human to the whole human (sub)population. Interspecies extrapolation consists of an allometric scaling factor and an EF for toxicokinetics and -dynamics. For the differences in toxicokinetics and -dynamics a default distribution was used, based on the results from Bokkers and Slob (2007). The allometric scaling depends on the average body weight of the experimental subjects and the average body weight of the target (sub)population. The intraspecies factor is set by expert judgment, expressed as a range for the factor between the average and sensitive (95^{th} percentile) of the human sensitivity distribution, where the range is wider for cases where the uncertainty in that estimated factor is larger (Van der Voet et al., in press). See below for a more extensive discussion. In the cadmium case some indirect information for the intraspecies factor for kidney dysfunction could be derived from the human data, although strictly speaking the variation in the effect measure does not directly translate into differences in sensitivity (which is defined on the dose scale). In the DON case an additional EF was applied to the male fertility effects to account for exposure duration effects.

No major obstacles were encountered in finding dose-response data in the case studies. In each of them good quality data on the relevant endpoints could be obtained. For DON, cadmium, the OPs, and T-2/HT-2 the dose-response data could be used on which the health based limit value (HBLV) of these compounds was based. If additional relevant endpoints were available they were included in the analysis. No HBLV has been derived for acrylamide. Therefore, data on the generally assumed relevant (i.e. neurological and reprotoxic) effects were selected based on our own expert judgment.

In the cadmium and OPs case studies specific analyses were performed to obtain CEDs. For cadmium a kinetic model was used to obtain doses in the appropriate dose metric. In the case of the OPs relative potency factors were derived from a combined dose-response analysis of the whole set of OPs in one single analysis. In general, no insuperable difficulties were encountered in the derivation of the PoD distributions.

The definition of the target (sub)population is important, and depends on both the effects to be expected, as on the real life exposure situation. This definition should therefore be established in close collaboration between toxicologists and exposure assessment experts. While performing the case studies, the discussions between these experts showed that the target (sub)populations may be selected based on various grounds. Based on the toxicological effects considered a (sub)population may contain one or both sexes and a particular age range. Some effects, such as decreased sperm count (DON), are only relevant in one of the sexes. Other effects are not sex specific, for example immune suppression (T-2/HT-2). In addition, some effects are only relevant in certain life stages. For example, reproduction toxicity is mainly considered in the reproductive age range, and effects on body weight probably have a high impact on children and juveniles. When the toxicity studies indicate acute effects and no particular sensitive subpopulations are known, then the choice of an age range can be based on knowledge or hypotheses about the exposure. For many compounds the exposure (per kg bw) is expected to be higher in children compared to adults. When considering acute effects we therefore used the exposure in a (sub)population of children (e.g. for OPs and T-2/HT-2).

In the current case studies we assumed that the intraspecies EF from is lognormally distributed. The intraspecies EF is characterized by a geometric mean (GM) equal to 1 and a geometric standard deviation (GSD) that needs to be given a value representing the intraspecies (human) variability (variation between persons in the population under consideration). The GM is 1 by definition and has no uncertainty. The uncertainty in this case relates to the GSD, as this statistic expressed the variation in the population. We assume that this uncertainty is described by a chi-square distribution with df degrees of freedom. A lower number of df represents higher uncertainty. Suppose that, for instance, an

expert opinion tells us: the sensitive individual that represents the 95th percentile of the human sensitivity distribution is between 2 and 10 times more sensitive than the average human. Here, the values 2 and 10 are to be interpreted as uncertainty bounds. It is proposed to consider this range of values as the 95 % confidence interval around the 'true' factor. This information can be translated into a best estimate of the GSD, and the value of df for expressing the uncertainty in that GSD, to be used as the statistical in put information needed in IPRA. For more details on this approach the reader is referred to Van der Voet et al. (in press).

5.2 Exposure characterization

The goal of the exposure characterization is to provide an IEXP distribution. The exposure assessments were performed for particular (sub)populations (Chapter 3). Exposure assessments of DON, cadmium, the OPs, and acrylamide have been performed previously (Boon et al., in prep.; De Winter-Sorkina et al., 2003). Therefore, no difficulties were encountered in these assessments. In contrast to the other compounds the concentration data on T-2/HT-2 in the Netherlands are scarce. Therefore, additional concentration data were obtained.

The exposure is estimated for (predefined) subpopulations in a particular age range. Further development of the methods could make the (subjective) choice of age range redundant. Then the IMoEs could be reported as a function of age. Nevertheless, it should always be decided which subpopulations are relevant, from a toxicological point of view, for deriving IMoEs.

5.3 Integrated probabilistic risk assessment

The CED distributions are extrapolated to ICED distributions using various extrapolation factors. Subsequently, ratios (IMoE) between the ICEDs and IEXPs are derived using Monte Carlo techniques. This procedure is automated and does not pose any problems provided that underlying data are present. When the underlying data are not available in the form of distributions, then data can be incorporated in the IPRA software as deterministic values. For example, when only a NOAEL is available, or when concentration data are limited. In those cases extra (quantitative or qualitative) uncertainty can and should be implemented.

The required time to perform a probabilistic risk assessment depends mainly on data availability, pre-existing knowledge of the compound in question, and additional data analysis. In the presented case studies the additional kinetic modeling in the cadmium case and the derivation of RPFs in the OPs case required relatively much time. Toxicity and exposure data and knowledge about DON, cadmium and the OPs were available, and did not pose a bottle-neck in the assessment of these compounds. Toxicity and exposure data and knowledge about T-2/HT-2 were less abundant. Therefore, the assessment of T-2/HT-2 was more time consuming than a relatively straight forward case, such as DON. Many carcinogenicity studies on acrylamide are available, but the non-carcinogenic effects of acrylamide are less well described. A methodology to assess carcinogenic effects is not implemented in the current probabilistic approach and it was relatively time consuming to analyze the relevant non-cancer effects. On the other hand, exposure data of good quality were available, making the assessment of acrylamide less time consuming compared to T-2/HT-2. In comparison to a probabilistic approach, a deterministic risk assessment is likely to be less time consuming. However, a deterministic approach lacks the

detailed results regarding the fraction of the population affected, severity of the effect, as well as the uncertainty analysis. This information can be obtained with a probabilistic approach and greatly improves the risk assessment, thus facilitating better informed risk management.

Presentation of the results
The resulting IMoE distribution describes the variability in the population due to underlying interindividual differences in intake of a compound and sensitivity to an effect. Various statistics of these results can be presented in several (graphical) ways. Furthermore, every statistic contains uncertainty, which can be presented in various ways as well.

In the results section of DON the results for one endpoint are presented as a cumulative distribution function of the IMoE (Figure 13). In addition the 90 % confidence interval for the IMoE cumulative distribution function is plotted. In principal all major risk characteristics and the uncertainty can be read from such a plot. However, the bar plots presented in this report are more concise, and give an overview of the results for the various endpoints that were considered relevant. These bar plots illustrate an important advantage over current risk assessment approaches: the decision of the most critical endpoint is now based not only on dose-response information, but also on the exposure information. It should be noted that it may happen that the endpoint with the largest human risk is not the endpoint with the lowest PoD in animals.
A choice can be made (beforehand) on which statistics should be presented to describe the variability of the IMoE. This choice depends on fraction of the (sub)population for which the risk assessment is required. Therefore, it should be decided upon in close consultation with the risk managers.

In Figure 29 the results of all endpoints of the five case studies are presented together in terms of the IMoE for the 1st percentile of the population and the associated 90 % confidence interval. From this figure it can be concluded that for most effects at least 99 % of the (sub)population is unlikely to be affected, since most confidence intervals do not include the value of one. For four effects, however, the confidence intervals do include the value of one, and in these cases more than 1 % of the population may be affected. Furthermore, it can be seen that from these four effects the uncertainties for the grip strength effects in acrylamide are larger than for the kidney effects in cadmium. This type of information may be used in deciding to take risk management measures or to do more research and try to improve the underlying data. If the latter is deemed appropriate, the figures presenting the relative contributions to the overall uncertainty are helpful (see e.g. Figure 28).

A disadvantage of Figure 29 is that in cases where the confidence interval around the 1st percentile of the IMoE distribution does not include one, it remains unknown what remaining small fraction of the population might still be affected. An alternative way of presenting the results is shown in Figure 30, where the percentage of the population with an IMoE smaller than one is plotted. This type of plot may be helpful in prioritization of compounds where risks cannot be excluded. For instance, the latter is the case for both cadmium and acrylamide, but the magnitude of the risks that cannot be excluded is much higher for acrylamide than for cadmium (see left panel of Figure 30).

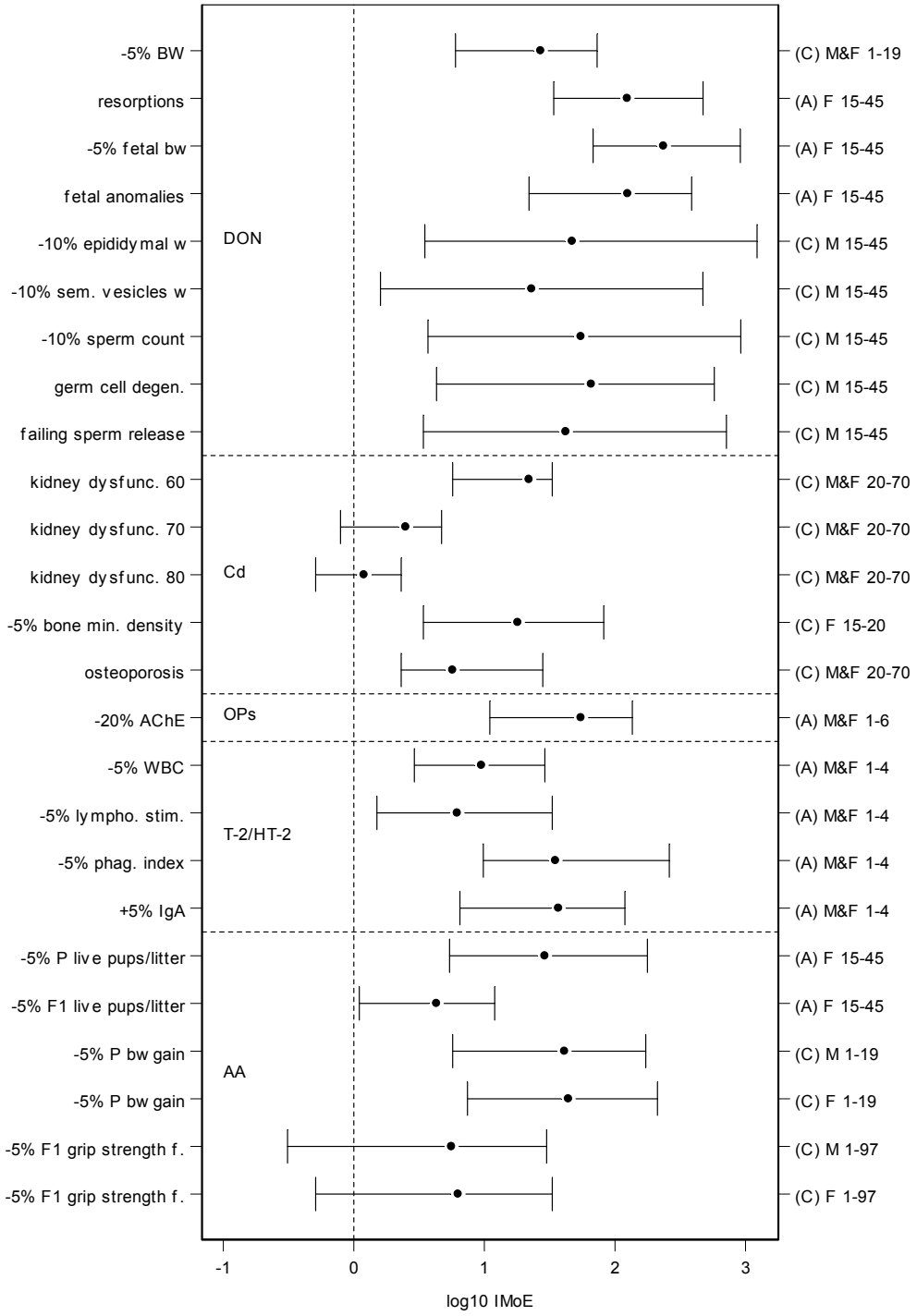


Figure 29. IMoEs for the effects induced by DON, cadmium (Cd), OPs, T-2/HT-2, and acrylamide (AA). The dots indicate the IMoE related to the 1st percentile of the population, and the whiskers indicate the associated 5 % lower and 95 % upper confidence bound. On the left y-axis the effect and the effect size (CES) are plotted. The right y-axis denotes the relevant subpopulation for which the (Acute or Chronic) exposure was derived. The vertical dotted line indicates the IMoE of 1.

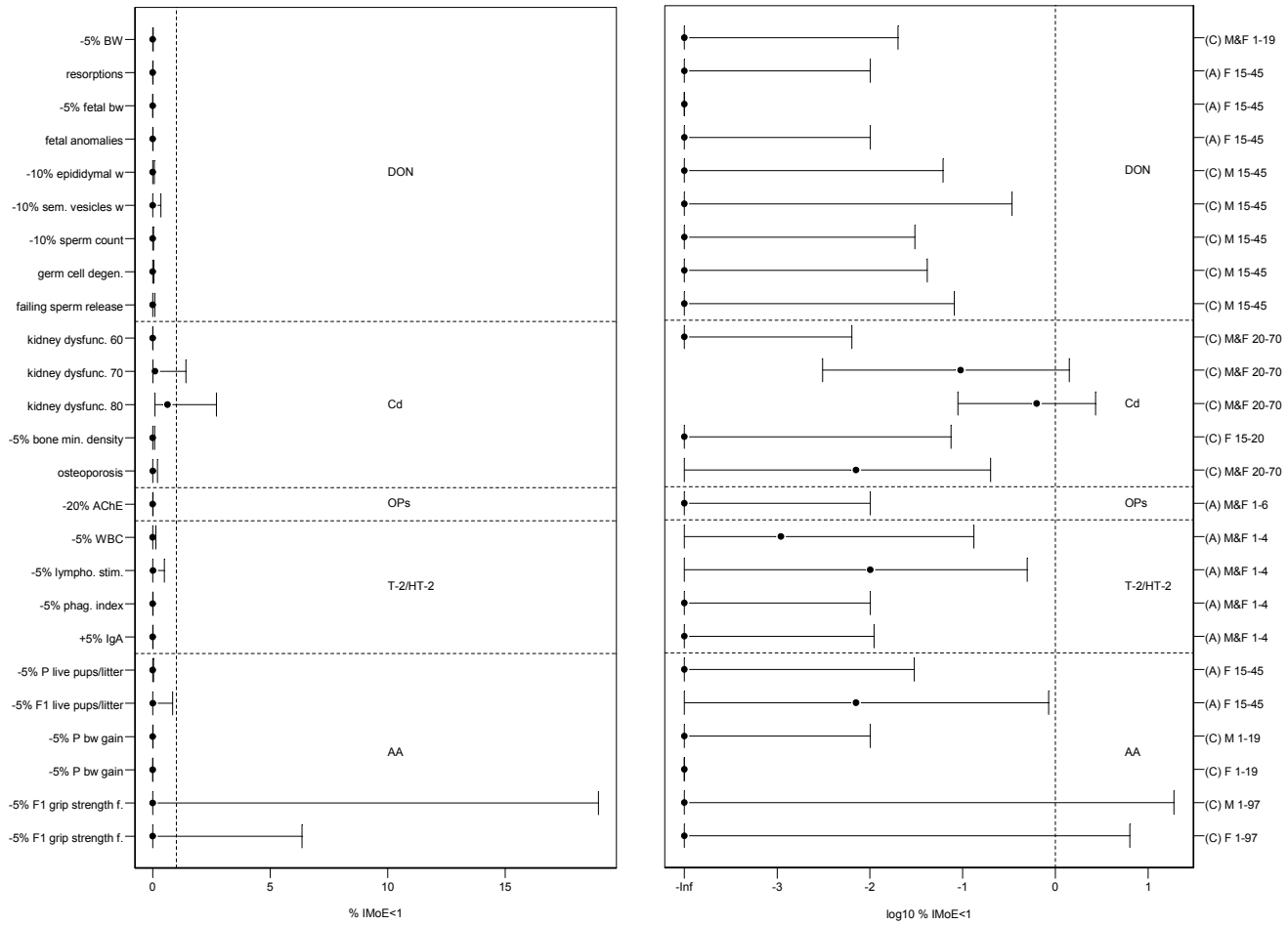


Figure 30. The dots indicate the percentage of the (sub)population with an IMoE below 1 on the natural (left) and log_{10} scale (right) and whiskers indicate the 5 % lower and 95 % upper confidence bound. On the left y-axis the effect and the exposure duration needed to produce the effect (Acute and Chronic) are plotted. The right y-axis denotes the relevant subpopulation for whom the exposure is derived. The vertical dotted line indicates 1 % of the subpopulation in both panels.

Comparing risks associated with different effects

Comparing the IMoEs within and between the case studies should be done with care. The effect sizes (CESs) are not explicitly set to be equally adverse. For example, it may be questioned if 10 % decrease in sperm count (in the DON case) is equally adverse to 5 % decrease in bone mineral density (in the cadmium case). Therefore, comparing the IMoEs of different effects requires expert toxicological and/or medical knowledge.

In addition, the use of both continuous and quantal responses in toxicology assessments hampers the ability to compare or prioritize effects. For continuous responses the severity of the effect is reflected by the specified critical effect size (CES). It may, for example, be concluded that the actual exposure to cadmium results in less than 5 % decrease in bone mineral density for at least 99 % of the subpopulation. For quantal responses this is somewhat different. Here the data do not allow a

statement about the degree or severity of the effect. For example; the actual exposure to cadmium leads to osteoporosis in less than 1 % of the population. Here the degree or severity of the osteoporosis is unknown. This is due to the fact that the researchers of the osteoporosis study have not reported their definition of osteoporosis, i.e. what level of the gradually changing process of osteoporosis is actually scored as osteoporosis. This problem appears in all reported quantal responses.

Prioritization of compounds, based on comparisons of distinct effects, may furthermore depend on the population affected. For example, prevention of effects in children or pregnant women may be given priority over effects in adults when they are considered equally adverse.

5.4 Uncertainties

The confidence intervals for the risk measures related to kidney dysfunction in the cadmium case are small compared to the intervals for other effects. This is partly due to the use of human data, so that interspecies extrapolation is not required. In this way one source of uncertainty is circumvented which results in a lower overall uncertainty for this effect.

In the IPRA software uncertainty analysis is an integral part of the risk assessment. There are numerous sources of uncertainty in risk assessment and the uncertainties can be substantial. It is recommended that these sources of uncertainty are identified and quantified as much as possible. However, it is neither practical nor necessary to conduct the most detailed uncertainty analysis in every risk assessment. The level of detail in the uncertainty analysis should be in line with the needs of the risk assessment (i.e. what question is addressed?).

Currently, the IPRA software incorporates the possibility to estimate the relative contributions of several sources of quantified uncertainty to the uncertainty in the final risk estimate. In the case studies presented here these sources were: the consumption data, the concentration data, the experimentally derived CED, the various extrapolation steps, and finally the Monte Carlo analysis itself. The contribution of these sources to the uncertainty is presented in each case study. It should be noted that the relative contributions may depend on the specific situation, such as the endpoint or the target population considered, and the specific risk characteristic (percentile or percentage, and which values). Therefore, in this report a fixed risk characteristic was chosen for which the relative contributions of the various sources are derived: the 1st percentile of the population.

The unquantified uncertainties should be described and discussed, for example using the tabular format proposed by EFSA (2006). Preferably some order of magnitude estimate should be given for the unquantified uncertainties relative to the quantified uncertainties. In the present case studies the possible presence of multiple exposure routes for cadmium (Oomen et al., 2007) exemplifies such additional uncertainties. If other routes have a significant contribution to the exposure then the risk of cadmium related effects will increase. As another example, the human data of cadmium are derived from an Asian population, who may be more sensitive to a decrease in bone mineral density (and thus osteoporosis) compared to Caucasians, because of their generally lower mineral density (Bachrach et al., 1999). The relative potency factors used in the assessment of the OPs are subject to unquantified uncertainty. The T-2/HT-2 concentration data contain unquantified uncertainty because correlated T-2 and HT-2 measurements were not available. A final example of unquantified uncertainty is the possible carcinogenic property of acrylamide. Assessing this property might result in a higher risk as compared to the noncancer effects considered in our case study.

Examples and guidance on methods to describe and discuss the unquantified uncertainties the reader is referred to EFSA et al. (2006), De Mul et al. (2008), and Van Ooijen et al. (in prep.).

Refining the risk assessment
The analysis of the contribution of several sources to the uncertainty enables a purposive reduction of the uncertainty in the risk assessment. The uncertainty contributions clearly indicates which uncertainty(/ies) should be addressed (in further research) to effectively reduce the uncertainty in the results. However, it should be noted that the reduction of uncertainty from some sources are more difficult and expensive than others. Therefore, feasibility should always be considered when aiming to reduce the uncertainty in a risk assessment.

6 Conclusions

The IPRA for each of the five compounds (DON, cadmium, the OPs, T-2/HT-2, and acrylamide) could be performed successfully. Toxicological and exposure data were available in sufficient detail. In some cases assumptions were needed to fill data gaps, which were considered reasonable (e.g. regarding the concentration data of T-2/HT-2). Additional analyses were needed in some cases, i.e. toxicokinetic modeling of cadmium concentrations in urine and the cumulative assessment of the OPs. These specific analyses could be easily included in the integrated probabilistic risk assessment.

It is expected that integrated probabilistic risk assessment is feasible for other compounds just as well, even when not all underlying data are available in the form of distributions. In fact, it may be argued that a probabilistic risk assessment has even more to gain in those situations where the data are relatively poor and the uncertainties large. When the additional uncertainties are quantified, the IPRA software can take them into account by translating them into the overall uncertainty in the final risk estimate. Making the uncertainties visible is obviously an advantage over deterministic approaches, where uncertainties might be ignored (as in a NOAEL that was based on weak data), or where they can be taken into account in an overly conservative way.

One feature that is not available in the current probabilistic approach is a methodology for assessing carcinogenic effects in a similar approach. Since these effects are often an important element in risk assessment and risk communication it is advised that more effort is taken to extend the integrated probabilistic risk assessment methodology for carcinogenic effects.

For a successful probabilistic and deterministic risk assessment the definition of the target (sub)population is paramount. The selection of the target population may be driven by the effects that were found in the toxicological database or the relevant exposure situation. Subsequently, the target population drives the input parameters, such as the allometric scaling factor, and the appropriate extrapolation factors, as well as the exposure scenario to be considered. In general, risk assessment should be performed and discussed in close collaboration with exposure assessment experts. As compared to a deterministic risk assessment there is a stronger impetus in a probabilistic assessment to match the exposure situation in the animal studies with the exposure scenarios in the human population in an early stage of the assessment. This is due to the explicit choices that need to be made for the various input parameters in the exposure assessment and hazard characterization.

The results of a probabilistic risk assessment can be presented in various ways. It is recommended that the format and statistics of the results are agreed upon prior to the actual calculations. Because the relevant format and statistics depend on the initial question it is expedient that the risk manager is involved in this decision. At the same time it should be made clear to the risk manager that there are limits to the outcome of the IPRA method that can still be reasonably estimated. These limits depend on the (quality of the) information available to perform the risk assessment.

The results of a probabilistic assessment facilitate the comparison of risks associated with the exposure to different substances. Furthermore, within one compound the risks of various effects can be compared. This can be particularly useful in either establishing priorities on further studies or in deciding to take risk management measures. However, these comparisons should be made with care, because prioritization may depend on various factors such as the quality of the effect, the degree of the

effect, the (sub)population at risk, and uncertainties in the assessment. In addition, other factors contribute in the decision: options for risk reduction measures, policy and societal aspects. Therefore, comparing the risks of different compounds or effects requires knowledge on toxicology, exposure assessment, risk assessment, and risk management.

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Abbreviations

A	acute exposure
AChE	acetylcholinesterase
AM	arithmetic mean
BBN	betabinomial-normal (exposure model)
BMD	benchmark dose
BMR	benchmark response
bw	body weight
C	chronic exposure
CED	critical effect dose
CES	critical effect size
DNFCS	Dutch national food consumption survey
df	degree(s) of freedom
DON	deoxynivalenol
EF	extrapolation factor
F	female
GD	gestation day
GM	geometric mean
GSD	geometric standard deviation
HLV	human limit value
ICED	individual critical effect dose
IEXP	individual exposure
IMoE	individual margin of exposure
IPRA	integrated probabilistic risk assessment
LL	lower confidence limit
LOR	limit of reporting
M	male
MC	Monte Carlo
OP	organophosphate
PoD	point of departure
Proc F	processing factor
Pxx	xx^{th} percentile (of a distribution)
RAC	raw agricultural commodity
SD	standard deviation
TD	toxicodynamic(s)
TDI	tolerable daily intake
TK	toxicokinetics(s)
UL	upper confidence limit

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