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The use of advanced risk assessment methods in answering various types of risk management questions
Why, when, and at what costs?

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Rapport in het kort

Het gebruik van geavanceerde risicoschattingsmethoden bij verschillende type beleidsvragen.
Waarom, wanneer en tegen welke kosten?

Er wordt nog onvoldoende gebruik gemaakt van nieuwe en geavanceerde methoden om blootstellingsrisico's van stoffen te bepalen. Dit terwijl het gebruik van geavanceerde methoden leidt tot meer realistische risicoschattingen. Hierdoor kan de verantwoordelijke riskmanager zijn aandacht (en budget) beter richten op die gevallen waar werkelijk sprake is van potentiële gezondheidseffecten. In een onderzoek van het RIVM zijn vijf *risk management* vragen zowel met klassieke methoden als met geavanceerde methoden behandeld. De geavanceerde methoden zijn de *Benchmark dosis benadering* en de *Probabilistische risicoschatting*. De geavanceerde methoden houden op een meer realistische en consistente wijze rekening met onzekerheden. Aanbevolen wordt om deze methoden in ieder geval toe te passen als de blootstelling aan een stof in de buurt ligt of hoger is dan de norm. Maar ook bij lagere blootstelling wordt toepassing van deze methoden aangeraden. De hieraan verbonden kosten zijn beperkt, indien geschikte software en de juiste expertise beschikbaar zijn.

Trefwoorden: benchmark dosis benadering, probabilistische risicoschatting, risk management

Abstract

The use of advanced risk assessment methods in answering various types of risk management questions
Why, when, and at what costs?

The risks of exposure to chemicals should be assessed more often by using new, more advanced methods. The use of these methods would lead to more realistic risk assessments which would facilitate the responsible risk manager in targeting his attention (and budget) to those situations where health effects are likely to occur. In a study of RIVM five types of risk management questions are approached with the classical methods as well with the Benchmark dose approach and probabilistic risk assessment. The more advanced methods aim to take the associated uncertainties into account in a more realistic and consistent way. It is concluded that the advanced methods are required when human exposure is higher than or close to the exposure limit (derived by the classical methods), while they are recommended when this distance is less than several orders of magnitude. The costs of applying these advanced methods (in terms of time needed for computer calculations) are limited, if suitable software and appropriate expertise is available.

Key words: benchmark dose approach, probabilistic risk assessment, risk management

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Samenvatting

De belangstelling voor nieuwe, meer geavanceerde methoden van *risk assessment*, zoals de Benchmark dosis benadering, en probabilistische risicoschatting, neemt steeds meer toe. De geavanceerde methoden houden op een meer realistische en consistente wijze rekening met onzekerheden. Dit rapport schetst, voor een vijftal typen *risk management* vragen, de essentie van de benadering door “klassieke” methoden en door meer geavanceerde methoden. De hier besproken geavanceerde methoden betreffen dosis-respons modellering, inclusief de benchmark dosis benadering, en probabilistische methoden toegepast bij zowel *exposure assessment* als bij *risk characterization.* Ook aan PBPK-modellering wordt aandacht besteed. Aangegeven wordt onder welke omstandigheden het de moeite loont om dergelijke meer geavanceerde methoden in te zetten en welke kosten (in extra tijd vanwege computer-modellering) hieraan verbonden zijn. Deze kosten zijn, vergeleken met het generen van de data, vrij beperkt, indien de geschikte software en de juiste expertise voor handen zijn.
In het algemeen kan gesteld worden dat de klassieke methoden van *risk assessment* goed voldoen zolang de (klassiek vastgestelde) blootstelling in de mens enkele orden van grootte lager is dan de (klassiek vastgestelde) blootstellinglimiet (bijvoorbeeld ADI). Wanneer de blootstelling in de mens hoger is dan deze blootstellinglimiet zijn geavanceerdere methoden noodzakelijk om een inschatting te maken over een eventueel gezondheidsrisico. In het tussengebied, waarbij de blootstelling in de mens lager is dan de blootstellinglimiet, maar minder dan enkele orden van grootte, zijn geavanceerde methoden toch aan te raden. De reden hiervoor is dat de klassieke benadering minder conservatief is dan vaak beweerd wordt, met name in het geval van zeer ernstige effecten zoals kanker en geboorte-afwijkingen.

Summary

There is an increasing interest for more advanced methods of risk assessment, such as the Benchmark dose approach and probabilistic risk assessment. The more advanced methods aim to take the associated uncertainties into account in a more realistic and consistent way. For each of five types of risk management questions, this report concisely reviews the essence of the classical risk assessment methods and of more advanced methods. For each of the types of risk management questions, the following advanced methods are considered: dose-response modelling and the Benchmark dose approach, probabilistic exposure assessment, and probabilistic hazard characterization. PBPK modelling is briefly discussed in a separate chapter. It is briefly indicated under which circumstances it is particularly useful to employ advanced methods, as well as the costs (in terms of time needed for computer calculations) that may be involved when applying them. In general, it may be expected that the costs of applying advanced methods are limited if suitable software and adequate expertise are available.
It is concluded that, in general, the classical methods suffice as long as their resulting exposure estimate in the human population is various orders of magnitude lower than their resulting exposure limit (e.g., ADI). When this estimated exposure is higher than the exposure limit that was assessed more advanced methods are required to estimate a potential human health risk. In the area in between, i.e., the classically derived exposure limit is less than several orders of magnitude higher than the estimated human exposure, advanced methods are yet recommended. The reason is that the classical method may not be as conservative as often suggested by risk assessors, in particular in the case of very serious effects like cancer or developmental malformations.

Glossary

ADI	Acceptable Daily Intake, also see RfD
AF	Assessment factor
ARfD	Aute Reference Dose
Assessment factors	also called safety factors, or uncertainty factors. Most frequently applied are the inter- and intraspecies extrapolation factors.
BMD	benchmark dose, i.e. a dose associated with a pre-specified (small) effect
BMDL	lower confidence limit of BMD
BMR	Benchmark response, the magnitude of the change in response for estimating the associated BMD. For quantal endpoints this is often 10% (extra risk). For continuous endpoints the term CES (Critical Effect Size) is used, which measures the degree of effect (e.g. 5% decrease in organ weight).
CED	Critical Effect Dose, the dose associated with some postulated CES.
CES	Critical Effect Size, used for continuous data. For instance, 20% inhibition of ChE activity.
DRM	Dose-response modeling
Extra risk	Additional risk (incidence at a given dose minus the background incidence) divided by the unaffected fraction of the population
Haber's rule	Assumes that an effect is proportional to the product of dose and exposure duration. Thus, halve the dose with double duration results in the same effect.
HBEL	Health-based exposure limit (in humans)
MAC	Maximum Allowed Concentration, used for workers
MOE	Margin of Exposure (human exposure divided by some toxicity dose level).
MRL	maximum residue level, used for residues of pesticides and veterinary drugs in food products
PoD	Point of Departure for further risk assessment, e.g., NOAEL, BMD(L). The assessment factors are applied to the PoD.
PRA	probabilistic risk assessment
probEA	probabilistic exposure assessment
probHC	probabilistic hazard characterization
probRfD	probabilistic reference dose
Risk characterization	assessment of HBELs or of dose-response in human target population
RfD	Reference Dose, or dose level that is considered save for humans
STEL	Short-term Exposure Limit, used for workers
TDI	Tolerable Daily Intake, also see RfD
T25	Rough estimate of dose level with 25% cancer risk, obtained by linear extrapolation from the first significant dose as observed in a carcinogenicity study
TEF	Toxicity equivalence factor, a factor expressing the relative toxic potential of two compounds
TLV	Threshold Limit Value, exposure limit used for workers
VSD	Virtually safe dose, used for cancer. It is derived by linear extrapolation starting from some dose with observable cancer risk, down to a low (non-observable) risk level, such as 10^{-6}.

1. Introduction

Over the last decades various new methods have been developed that have the potential to improve risk assessments as currently performed. This report aims to discuss the usefulness of these methods from the perspective of the risk manager. In chapter 2 a general discussion is given on why and when more advanced methods would be required. A more detailed discussion is given in chapter 4, where for a number of general types of risk management questions the main lines of the current ("classical") methods are summarized, and their main weaknesses are indicated. Then it is indicated how and under what circumstances more advanced methods may be expected to give a substantial improvement in answering the relevant risk management question.

The new methods that are considered here mainly concern the Benchmark dose approach, and various probabilistic methods (see chapter 3 for a brief discussion). PBPK modeling is also briefly discussed (chapter 5). In vitro methods are not considered here, as they do not improve risk estimates; their value lies in limitation of resources or animals used, usually at the expense of the quality of risk estimates.

The more advanced methods discussed here tend to be more expensive, but usually to a limited extent, as they involve computer work, and not data generation. Some indication will be given on the extent of additional work needed for the various methods.

Although much of the discussion in this report has a general nature, it has been written primarily for the situation of exposure to chemicals in food.

2. The need of more advanced methods

Current approaches of risk assessment are, from a quantitative point of view, quite simple. Transparency and easy application are advantages of such simple approaches. The disadvantage is that simple methods tend to result in rough estimates.

Most risk assessors would argue that the current methods are rough, but conservative. As a result, it is generally believed that in the situation where an HBEL (Health-Based Exposure Limit in humans) is not exceeded it can be assumed that health effects will not occur (or hardly so) in the human population. Only when an HBEL is exceeded, current methods would fail, as they do not tell to what extent human health effects might be expected in such a case.

While this point of view appears to be generally accepted, the underlying assumption that HBELs are conservative is unwarranted. Actually, it can be argued that they are not.
Some of the arguments are:

1. In the current approach, an HBEL is based on the NOAEL derived from animal studies. The NOAEL is usually mistaken as a dose without any effect at all. Only recently risk assessors start to realize that the NOAEL does not represent a “no-effect” level. Instead, the NOAEL represents a dose level where effects cannot be (statistically) distinguished. Depending on the quality (in particular, the size) of the study effects that can be distinguished may be small or large. Consider, as an example, a subchronic study, where typically ten animals (of both sexes) are used per dose group. Suppose that at the higher doses a significant increase in the incidence of some lesion is observed, while the lowest dose group shows no lesions at all. Clearly, the lowest dose will then be called a NOAEL (for that endpoint). However, for an observation on zero lesions out of ten animals, the upper (one-sided) 95%-confidence limit for the *true* incidence (i.e. the incidence for an infinite number of animals) at that dose amounts to 26%. In other words, an increase of that lesion by 26% cannot be excluded at this particular NOAEL. If this were the most sensitive endpoint for the compound, the HBEL would be based on a dose (overall NOAEL) where a 26% increase in incidence of the lesion cannot be excluded!
2. The NOAEL is usually divided by a factor of ten, to account for possible interspecies difference between the test animal and humans. This factor is often considered as conservative as well, but recent research shows that this is not the case. Detailed meta-analyses of historical toxicity dose-response data consistently show that the normal body-size scaling in terms of dose per kg body weight is inappropriate. Instead, the data show that (for oral administration) the dose should be scaled per kg body weight to some power (allometric scaling), where the value of the power should be somewhere around 0.7. As a consequence, the animal dose per kg body weight does not relate one-to-one to the human dose per kg body weight. To correct for this, the animal dose per kg BW should be divided by a correction factor, depending on the BW of the test animal. For the rat this factor would be around 5, and for the mouse even around 10. In other words, the current default factor of ten is hardly enough for just body size scaling. It is well recognised that different species can react very differently to the same chemical (in particular with respect to toxicokinetics), and using a default factor of ten for interspecies extrapolation to humans is clearly insufficient to result in protective human doses in most cases.

A second thing to keep in mind is that current approaches of exposure assessment are typically based on "point estimates" of the relevant quantities involved (i.e. the quantity is quantified by a single number). For instance, human exposure to chemicals in food is often estimated by combining a point estimate of a food's consumption rate with a point estimate of that food's concentration. Some exposure assessments use average values for these point estimates, others percentiles, and some use both of these, e.g., an extreme consumption rate is combined with an average concentration, or *vice versa*. As a result, the exposure estimates may relate to the best estimate of the average individual on an average day, or to a worst-case estimate of an extreme individual on an extreme day, or anything in between. Depending on what point estimates were used, the outcome of the associated risk assessment may be either conservative or anti-conservative. Frequently, however, this is not evaluated, and the exposure estimate is just considered as "the" human exposure. Therefore, it is unwarranted to regard a situation where the HBEL is not exceeded as "safe". Suppose, for instance, that the exposure estimate was based on the consumption behaviour of the average individual in the population. A substantial fraction of the population may then in fact exceed the HBEL.

The basic problem of the current approaches of risk assessment is that they result in rough estimates, while the assumption that they are (in general) conservative is unjustified and probably not true. Further, the level of conservatism (or the lack of it) is case specific.

It may be concluded that current (simple) methods of risk assessment may be regarded as sufficient as long as the associated human exposure level is far below the dose supposed to be without significant effects in humans. However, if the distance between human exposure and HBEL is not that large, current risk assessment approaches cannot be trusted. In that case, a more sophisticated assessment is in place, taking better account of the available information, as well as of the associated uncertainties. The more advanced methods are able to take the specific uncertainties into account on a case by case basis. The outcome of a more advanced risk assessment may be expected to be more reliable (less rough) than the current approaches, and may thus lead to different conclusions in individual risk assessments. Since the current methods contain both elements that are not sufficiently conservative and elements that are unnecessarily conservative, the use of more advanced methods will, on average, not necessarily result in more "expensive" outcomes. Rather, they may prevent that risk management costs are made in cases where they had not been necessary, and not made where they had been.

An important practical question that remains is: At what distance between exposure and HBEL (according to the current methods) are more advanced methods required? A single answer cannot be given, as it would depend on the situation. For instance, when the NOAEL relates to (serious) developmental malformations a much larger distance would be required to omit more advanced methods. Or, when the exposure was calculated based on worst-case point estimates, a smaller distance would be acceptable. Or, when the critical toxicity study was done in dogs, a smaller distance may be considered acceptable than had the study been done in mice. But, as a rule of thumb, when the distance is less than a factor of 100 more advanced methods appear desirable in most cases.

The additional costs of applying more advanced methods of risk assessment are, depending on the methods needed, minimal or mild. The main difficulty in getting the advanced methods being applied more commonly is the current lack of expertise among risk assessors. Therefore, training of risk assessors should receive major attention.

3. Advanced methods considered

This chapter briefly reviews the more advanced methods considered in this report.

probEA: Probabilistic Exposure Assessment
Application of statistical methods in assessing the exposure in the human population, with the (main) purpose of describing the variation between individuals, and/or for quantifying the uncertainty in the exposure estimates resulting from uncertainties in the underlying data.
Data needed
Food consumption survey data; these are available (for various western countries), and suitable for most compounds.
For long-term exposure assessment: average concentration in each relevant food.
For short-term exposure assessment: replicated concentrations in each relevant food.
Costs
One up to several days (computer work).

DRM: Dose-response modeling and BMD: Benchmark dose
Dose-response modeling is a method used for describing the dose-response over the whole (observed) dose range. The observed dose-response data are used for estimating a curve representing the estimated response as a function of dose. This curve may be used to predict the size of an effect at a given dose level, or for deriving a BMD.
The Benchmark dose has been introduced as an alternative to the NOAEL (i.e., for threshold effects). Since an effect of zero cannot be measured, a small effect size is chosen as a surrogate for zero effect. For quantal endpoints this small effect size is called a Benchmark response (BMR), for continuous endpoint Critical Effect Size (CES). After fitting a dose-response model, the dose associated with that BMR or CES is estimated (termed BMD and CED for quantal and continuous endpoints, respectively). Usually, the lower confidence limit of this estimated dose is considered as the Point of Departure (PoD).
For non-threshold effects the BMD(L) may be used as an alternative to currently used PoDs, such as the first significant dose, or to the T25.
Data needed (for DRM or BMD)
Dose-response data with at least three doses showing different effect levels is a minimum requirement.
Costs (for DRM or BMD)
Given that the dose-response data are available, a full BMD analysis of a complete toxicological study is more elaborate than a NOAEL analysis. Depending on the available data, a BMD analysis will cost several days. However, when the BMD methodology is also considered in designing the study, it may be expected to be more efficient, in the sense of getting more information out of the same number of animals used (or getting the same information out of less animals), see Slob et al. (2005).

probHC: Probabilistic Hazard Characterization
In probabilistic hazard characterization assessment factors are not applied as single numbers (e.g. 10), but in the form of distributions. These distributions represent the uncertainty in the factor. This approach results in a distribution of plausible “save” dose levels in humans. The probabilistic RfD (probRfD) is defined as a lower (usually 5^{th}) percentile of this latter distribution. Preferably this approach is combined with the BMD approach, but AF distributions may also be applied to the NOAEL.

Data needed
Instead of using default assessment factors a probHC can be performed by using default distributions for assessment factors, so additional data are not needed.
Costs
ProbHC can be done quickly (in the order of minutes), by using suitable software.

4. Risk management question and risk assessment methods

This chapter identifies five different types of risk management questions:

1. Deriving health-based exposure limits (HBEL)
2. Assessing actual risk at current exposure
3. Assessing potential risk when exceeding HBEL
4. Deriving product standards
5. Assessing risks from chemical mixtures

For each of these risk management questions the following aspects of risk assessment will be discussed:

- the main lines of the currently applied ("classical") methods,
- when the "classical" methods may be useful / sufficient,
- the main weaknesses of the classical methods,
- how the answer of the risk management question may be improved by more advanced methodology,
- when the use of more advanced methods is called for.

4.1 Deriving health-based exposure limits

Risk management question 1:
What level of exposure can be considered to be without appreciable health effects in the human (sub) population?

This type of question falls into the hazard characterization step of the risk assessment paradigm, and, in contrast to the other questions, no quantitative estimate of the human exposure is needed.

The following terms are typically used as HBELs (Health-Based Exposure Limits):

	Exposure limits = Exposure levels with no/low risk	
	General population	Workers
Long-term exposure	RfD/ADI/TDI	TLV / MAC
Acute exposure	ARfD	STEL

These HBELs (should) reflect *total* exposure levels (for a given route) for a given compound that would not result in (unacceptable) health risks. For instance, for dietary exposure, all

foods containing the compound should be taken into account. When various routes of exposure apply, these may (or should) be aggregated as well, although this is usually not easy (this is an example of a situation where PBPK modeling may be helpful, see chapter 6).

Long-term exposure limits are typically derived from studies with constant daily exposure. When exposure in humans in the real life situation fluctuates in time, the HBEL is often compared to the (arithmetic) mean exposure (per unit time), i.e., Haber's rule is assumed.

Long-term exposure limits are based on chronic studies (or subchronic if chronic studies are not available), acute exposure limits are based on acute or subacute studies. Acute studies usually do not (extensively) measure sublethal endpoints, and normally cannot be used for deriving HBELs.

4.1.1 Classical method

The classical approach of deriving exposure limits may be summarized as follows:

1. Is the compound assumed to have a dose threshold? If yes go to 2, if no go to 4

2. Assess NOAEL; this is the PoD
3. apply (default) assessment factors to PoD --- stop

4. PoD = lowest significant dose, or T25
5. either
   a. linearly extrapolate PoD to acceptable cancer risk level (=VSD), go to 6
   or
   b. assess MOE relative to PoD --- stop
6. do not apply assessment factors to VSD --- stop

Different assessment factors are used for the general population and for workers (in step 3). For the general population the VSD is based on a lower acceptable cancer risk level than for workers (in step 5).

When to use classical method

The classical method may be considered sufficient when the resulting HBEL is (at least) several orders of magnitude higher than the estimated exposure in humans.

Problems of Classical method

Classical methods result in an HBEL that is quite uncertain, while the degree of uncertainty is unknown. There appears to be a general belief among risk assessors that HBELs are conservative. However, as discussed in chapter 3, more deeply examining the underlying assumptions of the classical method indicates that this notion is not really supported by scientific arguments. Therefore, it cannot be excluded that the HBEL is not sufficiently protective, which is a relevant notion in situations where human exposure is not far lower (by less than several orders of magnitude, say) than the classically derived HBEL. See the next remarks illustrating that the currently derived HBEL may not be conservative (or might even be insufficiently protective).

The NOAEL represents a dose where no effects could be detected statistically. However, current study designs are not sensitive enough to detect all effects (in the sense of the magnitude, or degree of the effect) that may be toxicologically relevant. In other words, the

NOAEL might overestimate the dose where relevant effects start to occur. As an additional practical problem, many studies result in "LOAEL only", i.e., even the lowest dose applied results in (statistically) significant effects. The escape of treating the LOAEL divided by ten as a surrogate for the NOAEL may be overly conservative in some cases, but too liberal in others, without ever knowing this in any particular instance.

For serious effects (e.g., cancer with a nongenotoxic mode of action, developmental malformations) that are treated as threshold effects, the NOAEL could in fact represent a dose associated with an (extra) risk of 10% or more (given the sensitivity of the particular study design). Therefore, the NOAEL approach is debatable, in particular for serious effects: it might in some cases seriously underestimate risks.

The application of assessment (uncertainty) factors for each uncertain step in the overall risk assessment has the disadvantage that the level of conservatism associated with the HBEL is different for different compounds, depending on the availability of data for the particular compound. Thus, the level on conservatism remains unknown to the risk manager, who is thus unable to take uncertainties in risk estimates into account in decision making.

The default values of ten used for the assessment factors may not in all cases be sufficient. For instance, there is increasing evidence that expressing dose per kg body weight is not adequate. Extrapolating a dose in the test animal to an equivalent dose should probably be based on body weight to some power (around 0.75). In that case, a factor of ten would be hardly sufficient for extrapolating a dose in mice to an equivalent dose in humans. For rats, a factor of around 6 would be needed, leaving less than a factor of 2 for interspecies differences.

4.1.2 Possible improvements with advanced methods

BMD-approach

1. In step 2 of the classical method, use BMD(L) as PoD, instead of NOAEL (see, e.g., EHC, in prep., Edler et al. 2002)
2. In step 4 of the classical method, use BMD(L) (for 10% extra risk) as PoD, instead of significant dose (see, e.g., WHO Food Additives Series, in prep.)

Improvements:

- Results in better value for PoD than the NOAEL.
- Solves the "LOAEL only" problem.

probHC

3. In step 3 of the classical method, apply (default) assessment factors in terms of distributions (see, e.g., Slob and Pieters, 1998; Baird et al., 1996; Edler et al., 2002), resulting in ProbRfD.

Improvements:

- Avoids over-conservative nature of multiplying single (worst case) values.
- Better comparison among risk estimates, since both the "best" estimate and the uncertainty margins are available.

In the BMD (DRM) approach the distinction threshold vs. non-threshold plays no role in deriving a PoD. Instead, the crucial distinction is that between quantal effects (increased incidence) and continuous effects (increased degree of effect).

The choice of a relevant BMR (benchmark response) is crucial in the BMD approach. For quantal endpoints (e.g. incidence of liver lesions) the BMR is usually defined in terms of extra risk. For continuous endpoints (e.g. liver weights) the BMR (or CES) is usually defined in terms of a percent change compared to the average level in the controls. The choice of a CES in continuous endpoints is largely a scientific (toxicological) issue, while the choice of a BMR in quantal data seems to involve risk management choices.

The BMR or CES that is considered desirable (acceptable) may not always be observable. For instance, the acceptable risk level for cancer or developmental malformations may be much lower than the risk level that can be observed in a typical toxicity study. In those cases the BMR may be chosen purely based on the condition that it is observable. In the situation where the observable risk level is much larger than the desirable risk level, we are faced with the problem of low-dose extrapolation, which is an issue under debate. For continuous endpoints the low-dose extrapolation problem is less prominent: continuous dose-response data often allow for assessing a CED based on a CES that is both observable and (presumably) non-adverse.

At present, probHC uses distributions for assessment factors that have been proposed in the literature (Vermeire et al., 1999). Some of these distributions are data-based, others are based on assumptions (just like the current default factors of ten). Ongoing research tries to improve these distributions, by making them more data-based.

Quantal vs. continuous response data
Because of the fundamental differences between quantal and continuous endpoints, the implementation of advanced methods is somewhat different for quantal vs. continuous data, as indicated by the following schemes.

Advanced scheme for deriving HBEL: quantal endpoints (incidence of effect)

1. Derive the BMD(L) for BMR = 10%, if the dose-response data allow for that. (An even lower BMR might be chosen if the data allow this, but this will be rare).
2. Given the seriousness of the type of effect, decide if 10% extra risk is acceptable in a human population. If not, go to 3, else go to 4.
3. Apply a low-dose extrapolation factor to the PoD. Note: linear extrapolation may be considered as a conservative approach. Less conservative approaches are not available. Go to 4.
4. Apply (default) assessment factors in terms of distributions. (Note: apart from the interspecies factor, the intraspecies factor is needed as well, to take into account the potentially larger variation in the human population compared to the test animals in the lab.)

Advanced scheme for deriving HBEL: continuous endpoints (degree of effect)

1. Derive the BMD(L) for CES = 5%, if the dose-response data allow for that. (A higher CES might be chosen if the type of effect allows for that on biological grounds).
2. Apply (default) assessment factors in terms of distributions.

When to use advanced methods

BMD approach
From a scientific point of view the use of the BMD as a PoD is always better than a NOAEL, and the NOAEL would only be used when the dose-response data do not allow for dose-response modeling (e.g. too few dose groups with different effect levels).
Given that the dose-response data are available, a full BMD analysis of a toxicological study is more elaborate than a NOAEL analysis. However, when the BMD methodology is also considered in designing the study, it may be expected to be more efficient, in the sense of getting more information out of the same number of animals used (or getting the same information out of less animals), see Slob et al. (2005).

In the situation where an HBEL has already been derived, based on the classical method (i.e., based on a NOAEL), it may be considered to do a re-assessment based on the BMD approach when human exposure is close to the current HBEL.
A particular situation where the BMD can be usefully applied is when the most sensitive study / endpoint results in "LOAEL only". In many cases it will be possible to derive a BMD(L) for such data.

Based on experience so far, the BMD approach will, on average, not result in lower or higher values. In some cases the BMD is lower, in others higher than the NOAEL. However, the BMD gives a more precise estimate than the NOAEL.

ProbHC
Application of distributional AFs in deriving an HBEL could be applied for any standard assessment (nearly) without additional costs. The advantage of probHC is that it indicates the range of uncertainty of the "no-adverse-effect" dose in humans, and a (lower) percentile of that range could be chosen as a probabilistic HBEL (probRfD). In this way the level of conservatism can be taken into account by the risk manager. Further, probHC is useful if the risk manager wants to have similar levels of conservatism for a particular class of compounds. Or, on the other hand, different levels of conservatism might be considered appropriate for different compounds, depending on other interests that have various levels of importance.
A probHC can be applied in combination with the BMD approach by incorporating the uncertainty if the BMD estimate in the probabilistic assessment. In summary, various possible combinations of implementing advanced methods are:

	NOAEL	BMDL	BMD distribution
AFs (single values)	Classical method	BMD method	--
AF distributions	Partly probHC	--	Full probHC

4.2 Actual risk at current exposure

Risk management question 2:
Does a given compound result in (short-term or long-term) health effects for a particular (sub)population in the current real-life exposure situation?

Apart from hazard characterization exposure assessment is needed for answering this question.

For different populations (e.g., general population, children, workers) different exposure calculations are needed. Further, different acceptable risk levels or different assessment factors may be used in the risk characterization.

Distinction long-term or short-term is relevant for:

a. Exposure calculations:
- calculate average exposure over time (within individuals),
- or calculate (extreme) exposures during short period (e.g. one day)

b. Selection of chronic vs. acute HBEL, i.e., exposure limits are based on long-term or on short-term studies (e.g., ADI vs. ARfD).

The situation of chronic (long-term) and acute (short-term) effects will be discussed consecutively.

4.2.1 Chronic effects

Risk management question 2a:
Does a given compound result in long-term health effects for a particular (sub)population in the current real-life exposure situation?

Chronic risk assessment relates to effects after long-term exposure. Therefore, human exposure is compared to an HBEL derived from effects measured in long-term exposure studies. Long-term animal studies typically apply constant (daily) doses to the animals. In real life human exposure fluctuates, in some cases moderately (e.g., dietary intake of dioxins), in other cases heavily (e.g., pesticides in apples). In cases where an individual's exposure is zero on many days, and high on few days, the average (arithmetic mean) exposure over a longer period is assumed to reflect the appropriate exposure measure for chronic effect, but it remains unclear if this assumption (Haber's rule) is valid in any particular instance.

4.2.1.1 Classical method

The classical approach of assessing actual risks related to chronic effects may be summarized as follows:

1. Calculate average exposure in the relevant (sub)population. For dietary intakes, multiply average concentration with average consumption of each relevant food and sum the resulting products.
2. Compare average exposure with a chronic HBEL (ADI, RfD).
3. either
   a. if exposure < HBEL → no risk, else → there might be a risk, but we do not (really) know
   or
   b. calculate MOE (ratio of exposure to PoD), and use this value as an indication of potential risk

When to use classical method

The classical method may be considered sufficient when the HBEL is several orders of magnitude higher than the estimated (average) exposure in humans.

Problems of classical method

Step 1 calculates the average exposure in the population. Knowing the average exposure may not be sufficient because exposure varies among individuals. To protect the "whole" population, the exposure of non-average individuals (e.g., with non-average consumption behavior) should be taken into account as well.
Further, all problems related to deriving a HBEL (see chapter 3.1) apply here as well.

4.2.1.2 Possible improvements with new methods

For a given exposure level that may result in human health effects, some people will show minimal, others mild, and still others severe health effects. Therefore, ideally, health effects at current exposure levels should be described as a two-dimensional picture: incidence (fraction of the population) as a function of the severity of effects evoked. This is not easy, given the limited data we usually have, while methods of doing this have not been published. Hence, current advanced methods either focus on incidence (estimate the fraction in the population exceeding a given exposure limit), or on degree of effect (estimate the degree of an effect in the sensitive subpopulation). The following improvements may be achieved by using advanced methods:

ProbEA:

1. Estimate the distribution of long-term exposures in the individual of the population (e.g. Slob, 1993; Nusser et al., 1996; Slob, 2005). Calculate the fraction of the exposure distribution exceeding the HBEL (e.g., Liem et al., 1991).

ProbHC:

2. At a given exposure level (point estimate)
   either
   estimate the probability (incidence) of a given effect (e.g. Evans et al., 2001),
   or
   estimate the (range in the) degree of a given effect (e.g. Pieters et al., 2004).

ProbEA + ProbHC:

3. Apply option 2 for a particular percentile of an exposure distribution assessed by probEA (e.g., Pieters et al., 2004).

ProbEA + ProbHC:

4. Derive a probRfD as an HBEL (see chapter 1) and calculate the fraction of the exposure distribution exceeding this probRfD (i.e., use probabilistic HBEL in option 1)

Integrated PRA:

5. Integrate the exposure distribution with the distribution underlying the probRfD, and determine a distribution of MOE, where MOE = 1 refers to no risk (e.g., Van de Voet and Slob, subm). In this approach both (true) variation and uncertainty are taken into account for both EA and for HC.

When to use advanced methods

Advanced methods are required when, in step 3 of the classical method, the estimated exposure exceeds the HBEL. However, it is also recommended to apply advanced methods when the exposure is less than several orders of magnitude lower than the HBEL.
The application of probHC (i.e., use advanced methods for deriving an HBEL, see chapter 3.1) deserves first priority. For compounds that occur in various (basic) foods (so that intake is nonzero on all days) the effect of probEA is relatively mild, since the variation in long-term exposure among individuals is usually relatively small. However, for compounds that occur in incidentally consumed products, the variation in exposure could be much larger.

4.2.2 Acute effects

Risk management question 2b:
Does a given compound result in short-term health effects for a particular (sub)population in the current real-life exposure situation?

Acute effects are related to short-term (peak) exposures. For dietary exposure this usually relates to incidental consumption or incidentally high consumption of a particular (non-basic) food, possibly in combination with an incidentally high concentration of the compound.
A relevant short-term exposure period depends on the situation. In the discussion below ‘one day’ will be used to indicate a short-term exposure period, but any other (short) period can be substituted.

4.2.2.1 Classical method

The classical approach of assessing actual risks related to acute effects may be summarized as follows:

1. Estimate extreme potential exposure for one day, using worst-case assumptions (e.g., assume very large portion of food consumption on a single day, and choose highest concentration ever measured in the relevant food)
2. Compare worst-case exposure with ARfD. Choose from 3a and 3b.
3 either
   a. if exposure < ARfD → no risk, else → there might be a risk, but we do not (really) know

   or

   b. calculate MOE (ratio of exposure to PoD), and use this value as an indication of risk

When to use classical method
The classical method may be considered sufficient when the HBEL (ARfD) is substantially higher than the estimated worst case peak exposure in humans.

Problems of classical method
The worst-case estimate of a peak exposure may be unrealistic, and this may lead to overestimation of health risks. This problem is even more prominent when the compound occurs in various foods, while it is assumed that all these foods are consumed (in large portions) simultaneously or on the same day. While it is clear that such is highly unrealistic, it remains unclear how to get to more realistic estimates without applying probabilistic methods.
Further, all problems related to deriving an HBEL (see chapter 3.1) apply.

4.2.2.2 Possible improvements with advanced methods
Acute exposures do not only vary between individuals, but they also fluctuate in time within the same individuals. For instance, intake via food varies not only between individuals but also between days within individuals. This distinction may be either ignored or taken into account. Both situations are discussed below.

Variation in exposure between and within individuals taken together

ProbEA
1. Determine the distribution of short-term exposures by lumping all observed or calculated exposures in a single distribution (e.g. MCRA, see Van der Voet et al. 2003). Calculate the fraction of the exposure distribution exceeding the ARfD.

ProbHC
2. Estimate a worst-case short-term exposure (e.g. based on large portion) and estimate the associated incidence or the (range in the) degree of an effect based on short-term toxicity data using dose-response modeling and probabilistic AFs.

ProbEA + ProbHC
3. Derive a ProbARfD as an HBEL (see chapter 1) and calculate the fraction of the exposure distribution exceeding this ProbARfD (i.e. option 1 after replacing ARfD by ProbARfD).

Integrated PRA
4. Compare the exposure distribution with the distribution underlying the ProbARfD, and, by taking the ratio of these two distributions, determine a distribution of MOE, where MOE = 1 refers to no risk. (Van der Voet and Slob, subm). In this approach both (true) variation and uncertainty are taken into account for both EA and for HC.

Note: the distributions resulting from any of these options relate to person-days, i.e. any fraction of the distribution relates to person-days. A fraction of person-days is only limited information. For instance, a fraction person-days of 5% may result from all days in 5% of the individuals, or to 5% of the days in all individuals, or anything in between.

Variation in exposure between and within individuals separated

Distinguishing between the variation among persons and among days requires probEA. Therefore, the second option just described (ProbHC only) does not occur here.

ProbEA

1. Determine the distribution of short-term exposures such that the variation between persons and the variation between days (in the same individual) is quantified separately. Calculate the distribution of the fraction of days at which the ARfD is exceeded. This distribution can be interpreted as representing the variation among individuals in the population, i.e. it indicates what fraction of the population exceeds the ARfD at a particular fraction of days.

ProbEA + ProbHC

2. Same as option 1 but replace ARfD with ProbARfD.

Integrated PRA, with BMD serving as no-adverse-effect level

3. Integrate the exposure distribution with a probabilistic (continuous) dose-response model, and determine a distribution of MOE at the level of the individual, where MOE = 1 refers to no risk. This approach has not yet been worked out.

Note: More options are conceivable, but have not been developed in any detail.

When to use advanced methods

Advanced methods are required when, in step 3 of the classical method, the estimated exposure exceeds the HBEL. However, it is also recommended to apply advanced methods when the exposure is less than several orders of magnitude lower than the HBEL.
The application of probEA is for question 2b (acute effects) more important than it is for question 2a (chronic effects).

4.3 Potential risk when exceeding health-based limits

Risk management question 3:
Given the observation that the measured (estimated) exposure exceeds the HBEL, is there a health risk associated with that exposure?

4.3.1 Classical method

The classical approach of risk assessment does not allow for quantitative estimation of potential risks when HBELs are exceeded. To quantify potential risks above an HBEL, BMD and/or probabilistic methods are required.

4.3.2 Possible improvements with advanced methods

It should be noted that estimating the risk at an exposure level that exceeds the HBEL is not basically different from estimating the risk at current exposure levels discussed in chapter 3.2. Therefore, the approaches in chapter 3.2 are in fact equally applicable.

Below, some situations of finalized risks assessments are described, based on classical methods only, or partly based on advanced methods. It is indicated what (further) advanced methods would be most effective in improving the result from that situation of applied risk assessment. It is assumed that there are no significant data gaps; if there are, other steps than indicated here might be more effective.

A (point) estimate of the average (long-term) exposure is found to exceed the (chronic) HBEL.
ProbHC
In this situation, applying ProbHC is probably more effective than applying ProbEA, since the variation in long-term exposure is usually small compared to the uncertainty in the HBEL. Applying ProbHC will result in a probability (incidence) of a given quantal effect in the human population, or in an uncertainty range of the degree of a continuous endpoint.

A (point) estimate of a worst case peak exposure is found to exceed the ARfD.
ProbHC
Assess the probability (incidence) of a particular quantal effect, or the uncertainty range in the degree of a continuous effect at that exposure level using dose-response data from short-term studies.

A ProbEA results in a long-term exposure distribution that partly exceeds the (chronic) HBEL.
ProbHC (+ ProbEA, already performed)
There are two options here:

1. Derive a ProbRfD and assess the fraction of the exposure distribution exceeding this limit

Integrated PRA

2. Assess the distribution of the MOE by dividing the distributions of human exposure and human no-effect-level

A ProbEA results in a distribution of short-term exposures that partly exceed the (acute) HBEL.
There are two options here:
ProbHC(+ ProbEA, already performed)

1. Derive a ProbARfD and assess the fraction of the exposure distribution exceeding this limit (either distinguishing between inter-individual and inter-day variation, or not; see chapter 3.2).

Integrated PRA

2. Assess the distribution of the MOE by dividing the distributions of human exposure and human no-effect-level (either distinguishing between inter-individual and inter-day variation, or not; see chapter 3.2).

When to use advanced methods
In fact, the risk management question of estimating risks at current exposure can, strictly speaking, not be answered by the classical methods, and advanced methods are always needed here.

4.4 Deriving standards

Current methods of deriving product or environmental standards are quite variable, depending on type of compound (framework) and type of product or environmental compartment. Different frameworks often use different assumptions, while different standards for the same compound (e.g. in different products, foods or environmental

compartments) are typically assessed independently form each other, so that they may not be consistent with each other.

In this chapter we restrict ourselves to standards for food products, related to food additives, veterinary drugs, pesticides, and contaminants.

Risk assessment question 4:
At what (maximum) concentration in a given (food) product can adverse health effects be excluded in the human population?

This question applies to food additives, contaminants, veterinary drugs, and compounds in packaging material. The answer to this question is directly related to the setting of a standard. For pesticides, however, the situation is slightly different. Here, the value of a standard is primarily based on other grounds (application of the pesticide according to good agricultural practice), but before this value is implemented as a legal Maximum Residu Level (MRL), it needs to be assessed that this value does not lead to health effects. Hence, the question for pesticides is slightly different:

Risk assessment question 4a:
Does the proposed (limit) concentration in a given food product lead to adverse health effects in humans?

The second question only requires a yes-or-no answer, while the first question requires a quantitative answer.

Most standards are derived for the situation of chronic effects due to long-term exposure. For pesticides, however, acute effects following short-term exposure are often relevant as well.

For veterinary drugs an additional complication is the waiting time: the minimal time interval between last application of the drug and slaughter. A similar complication may be at stake for pesticides (time between pesticide application and consumption of the product).

4.4.1 Classical method

The basic approach of deriving a food standard is to calculate the concentration in the food product such that human intake does not exceed the ADI/TDI. In practice, assumptions are made regarding human food consumption, and often these assumptions are worst case. For the purpose of marketing authorization (in Dutch: *toelatingsbeleid*) of food additives or veterinary drugs these worst-case assumptions are considered appropriate, and the resulting conservative standards are accepted as such. For pesticides, however, there is a tendency to search for more advanced methods, in particular in cases where the conservative approach would lead to rejection of the subscription.

For contaminants conservative standards may in some cases be hard to realize, while the costs that need to be made to maintain low standards may not be (directly) related to those who caused the contamination. Therefore, in deriving standards for contaminants, more “realistic” assumptions are normally applied, such as using an average daily food package rather than an extreme food package.

When to use the classical method
For food additives and veterinary drugs the standards may be expected to be quite conservative, given the conservative exposure estimates that are used. When the stakeholders accept these conservative estimates produced by the classical methods there is no direct reason to use advanced methods. It should be noted, however, that the classical HBEL may in some cases not be conservative (see chapter 3.1), and it needs to be considered in any particular instance if the classically derived HBEL can indeed be regarded as conservative. In case of doubt, a probHC may be called for.

Problems of classical method
The notion that the classically derived HBEL is probably conservative is an assumption that is not firmly based on scientific arguments. In fact, it might not be sufficiently protective in some cases, as already discussed (chapter 3.1).
The classically derived exposure estimates, on the other hand, are usually quite conservative. It should be noted however, that classical methods estimate average exposure in the human population. Therefore, individuals with higher than average exposure might not be protected.

Deriving standards for different food products but for the same compound by classical methods is problematic. Either, total exposure from simultaneous consumption of the different products is not considered (which will be anti-conservative) or it is assumed that all products are consumed on exactly the same point in time (which will often be unrealistic, resulting in overly conservative standards).

4.4.2 Possible improvements with advanced methods

Deriving product standards is similar to estimating actual risk at current exposure levels, as discussed in chapter 3.2. The only difference is that, instead of using the observed or estimated real life concentrations in all products, the concentration(s) in the product(s) at stake are now modulated in the calculations until the resulting risk is acceptably small or negligible. Thus, all advanced methods discussed in chapter 3.2 equally apply to the derivation of product standards.

The derivation of standards for different products (for the same compound) can be improved by probEA where simultaneous consumption of different products on the same day is taken into account in a realistic way. In this way one may estimate the exposure distribution when all products always have a concentration at the maximum allowed (standard) level. Or one may also want to take into account that concentrations vary and will not be at their maximum allowed level on every day. For instance, for pesticides a range of concentrations is typically available from supervised field trials, and these could be used for estimating a distribution of realistic concentrations on the products.

When to use advanced methods
For contaminants the setting of standards is often quite critical in the sense that they should neither be unnecessarily low nor unnecessarily high. Thus, new methods are most useful in the field of contaminants. For instance, in setting a dioxin standard for cow's milk, ProbEA was applied to take account of the interindividual variation in the Dutch food consumption behavior (Liem et al.,1991).

For pesticides new methods are useful in situations where the proposed MRL (based on good agricultural practice) might involve health risks according to the classical methods.

ProbEA is particularly useful when standards for different products (for the same compound) need to be set. With these methods, a realistic estimate of the probability of simultaneous exposure can be made.

4.5 Chemical mixtures

Any of the risk manager questions discussed in the previous chapters may be extended to a situation where the exposure relates to a mixture of chemicals. Individuals are exposed to numerous chemicals all the time (including the abundant chemicals naturally occurring in food), and some restriction as to what defines a mixture is necessary. In risk assessment, mixtures usually relate to chemicals having a similar mechanism of action, resulting in a similar type of effect. Usually, such chemicals have structural similarities as well. Some famous examples are: dioxins/furans/coplanar PCBs (binding to AH receptor), and organophosphate-esters/carbamates (binding to cholinesterase).

For chemicals with different mechanisms of action it is usually assumed that combined exposures that are individually below (or near) the no-effect levels of the pertinent chemicals would normally not result in effects, when the individual effects are not related to each other. It remains unclear if this assumption is realistic in any particular instance (Health Council of the Netherlands, 2002).

For chemicals with similar mechanisms of action the principle of “dose addition” is often assumed, which means that the doses of the individual compounds can be added together, after scaling these doses by their relative toxicity (=toxicity equivalence factors, TEF). This assumption has not been sufficiently validated.

4.5.1 Classical methods

When dose addition is assumed, toxicity equivalence factors (TEFs) are derived by assessing TEFs choosing a reference compound (e.g. the most toxic, or the best studied one) and by taking its NOAEL as a reference value. This NOAEL is divided by that of any related compound, representing the TEF for that compound.
An HBEL for a mixture is derived by assessing an HBEL for the reference compound in the usual way. The HBEL for the mixture is expressed in toxicity equivalents (TEQs) for that reference compound.
Risk at current exposure is assessed by multiplying the exposure to each individual compound by its TEF, and by taking the sum of the products. The result is an exposure level in TEQs. This “total” exposure is compared to the NOAEL of the reference compound.
Standards are derived by expressing the concentration of the mixture in terms of the reference compound, after deriving a standard in the same way as for a single compound.

Problems of classical methods

NOAELs contain errors, and TEFs contain even more error (due to accumulation of the errors in the numerator and the denominator). For some compounds, a NOAEL cannot be assessed ("LOAEL only"), and in these cases the TEF is particularly unreliable.
For assessing an HBEL the same problems apply as discussed in chapter 3.1.
For acute effects, it is not possible to make a realistic estimate of a combined exposure, only worst-case exposure estimates can be produced (e.g., assuming that the different compounds simultaneously occur in the different products consumed on the same day). Therefore, risk at current exposures cannot be assessed for acute effects.

4.5.2 Possible improvements with advanced methods

DRM
With DRM it is possible to assess the TEFs for all relevant compounds in a single analysis. In this way all data are used efficiently. In addition, it is possible to estimate the (statistical) errors in the TEFs. Of course, the dose response data for the different compounds need to have the property that their TEFs do not depend on the response level. This assumption can be accurately checked by DRM.

ProbEA
Variation of concentrations in products, and realistic variation in consumption of products, including their combined occurrence, can be taken into account, resulting in distributions of exposure in terms of the reference compound.

5. PBPK modeling

In the classical approach, the PoD is directly based on the relationship between external dose and effect, usually observed in the animal. If toxicokinetic information is available this is rarely used in the quantitative derivation of a PoD.

PBPK modeling has been proposed to improve the extrapolation of animals to humans by translating an internal dose (associated with the PoD) in the animal to an analogous internal dose in humans. In this way, possible differences in toxicokinetics between the test animal and humans may be quantitatively accounted for, resulting in more reliable HBELs.

When to use PBPK modeling
PBPK modeling is quite expensive, both in terms of generating data and in terms of modeling. It is therefore not suitable for large-scale application in standard assessments . It would primarily be useful for compounds where exposure is close to effect levels, while reduction of human exposure is expensive or difficult to realize.
For a successful and reliable application of PBPK modeling with the purpose of improving risk assessment for a specific compound, date on human toxicokinetics would be needed as well.
The human PBPK model for dioxins is a rare example of a human PBPK model (validated with human data) that can be successfully used for risk assessment (Van der Molen et al., 2000).

Other applications of PBPK modeling
PBPK modeling may be used in gaining general insights, e.g., what conditions are required for having dose-addition of mixtures, how do resistant compounds behave in general, etc.

Further, in the context of replacing *in vivo* effect studies by *in vitro* effect studies, PBPK modeling (or toxicokinetic modeling in general) will be needed to translate local (*in vitro*) concentrations to external (*in* vivo) dose levels.

6. Conclusions

The widespread belief that HBELs as currently derived by the classical methods are conservative is unjustified, and, at least in part of the cases, inappropriate. It might in some cases (in particular for serious effects as cancer, malformations or mortality of neonates) overestimate the human dose level that is supposed to be without appreciable health effects in the human population. This possibility relates to all risk management questions discussed here.

Therefore, the situation where human exposure is just below the HBEL does not justify the conclusion of “no risk”, and application of the more advanced methods is required to better support any conclusion to be drawn. Only when exposure is remote from the HBEL, more advanced methods may be omitted.

The use of the BMD approach would theoretically be better than the NOAEL approach in all cases of risk assessment, leading to more reliable answers to the risk management questions. However, given the additional (time) costs, one might consider to use the BMD approach only when the classical approach leads to a relatively small distance between the HBEL and human exposure. It is hard to give guidance on a quantitative value for that distance, but it seems warranted to omit the BMD approach (or probHC in a broader sense) when human exposure is more than several orders of magnitude lower than the classically derived HBEL.

The application of probabilistic assessment factors (ProbHC) involves hardly any additional costs, and could easily be done in addition to current risk assessments. The results give insight into the uncertainty margins of a particular HBEL, which is useful information for the risk manager.

For intakes of chemicals by food probabilistic exposure assessments can be done relatively easily as well. The calculations involved require a limited amount of time (in the order of days), if the suitable software is available. For chronic exposure, probabilistic assessments will not always result in dramatically different conclusions compared to the classical approach, since the variation among individuals in long-term intakes has been found to be relatively small for the compounds considered so far. Probabilistic exposure assessment appears particularly relevant for acute exposures.

The additional costs of applying more advanced methods of risk assessment are, depending on the methods needed, minimal or mild. The main difficulty in getting the advanced methods being applied more commonly is the current lack of expertise among risk assessors. Therefore, training of risk assessors should receive major attention.

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