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The Risk Thermometer

– *A tool for risk comparison*

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Content

List of abbreviations

AF	Assessment factor
BMD	Benchmark dose
BMDL	Lower 95 % confidence bound on the benchmark dose
BMR	Benchmark response
DALY	Disability-adjusted life year
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
HBGV	Health-based guidance value
MOE	Margin of exposure
NFA	Swedish National Food Agency
NOAEL	No-observed-adverse effect level
PARP	Population-adjusted reference point
POD	Point of departure
RP	Reference point
SARP	Severity-adjusted reference point
SAMOE	Severity-adjusted margin of exposure
SF	Severity factor

Summary

In this project, the first version of the Risk Thermometer for comparison of chemical risks associated with chronic exposure via food (i.e., not acute effects) has been developed. This tool can for example be used to assess and compare exposures to environmental contaminants, pesticides, food additives, chemicals used in food contact materials, as well as minerals/nutrients. A public consultation on the draft report on the Risk Thermometer was held between 2014-12-17 and 2015-02-28. The public consultation helped to improve the final product.

The Risk Thermometer consists of four parts: 1) a severity-adjusted margin of exposure (SAMOE) approach, which is an extension of the present approach for chemical risk characterization, 2) a model that describes the uncertainty in the SAMOE, 3) a risk classification approach that categorizes the SAMOE value in terms of health concern levels, and 4) a graphical illustration of the results. The present report focuses on the underlying parts (1, 2, and 3) of the Risk Thermometer, and while examples of illustrations are included the graphical front end of the tool (part 4) will be further developed.

By choice the Risk Thermometer is based on both scientific considerations (risk assessment) and value-based considerations (risk management). The tool is regarded to bridge the three elements of risk analysis (risk assessment, risk management, and risk communication. It is, however, in line with the important principle of an operational separation between the three sectors.

The Risk Thermometer provides the Swedish National Food Agency (NFA) with a new approach for priority-setting, and contributes for example to the further development of a risk-based food control. Importantly, results from the Risk Thermometer represent one basis for risk management. For example, they apply to the target population under investigation. Thus, aspects of total public health burden, taking population size into consideration is not explicitly included. Such factors need to be accounted for separately as part of further risk management.

The Risk Thermometer also aims to communicate levels of risks to consumers, the media, and other stakeholders, and it is anticipated that it will clarify the results of quantitative risk assessments performed by the NFA. As noted above, the graphical illustration of the results (part 4 of the tool) that relates to risk communication will be further developed. In general, updates of the Risk Thermometer will be considered as experience of using this approach in the process of risk analysis increases.

To satisfy the objectives of the Risk Thermometer a framework for comparative risk characterization has been developed that efficiently can be integrated in today’s risk assessment, risk management, and risk communication workflow at the

NFA. Such a practical framework needs to be based on current risk assessment methodology, including data requirements as well the use of default values (e.g., adjustment factors, AFs), to a high extent. These considerations have been important for the selection and design of the SAMOE approach.

The minimum data requirement for the SAMOE approach is 1) an estimate of the exposure to a chemical in the target population, and 2) a reference point (RP) like the benchmark dose (BMD). These are the main inputs currently used for quantitative risk characterization of chemicals where an RP, or similar, is compared to the exposure using the margin of exposure (MOE), or MOE related concept. Thus, for chemicals the risk is generally described by a MOE. The MOE indirectly relates to the probability of occurrence (or change in the response) of a health effect. However, the severity of the health effect is also an important element of the risk concept which is generally not accounted for by the MOE. This consideration is of particular relevance herein since the objective of the Risk Thermometer involves comparative risk characterization across chemicals and health effects in contrast to applications of the traditional MOE approach.

The SAMOE approach addresses this issue by penalizing the traditional MOE value depending on the severity of the critical health effect used as basis for risk assessment. This is achieved by the systematic use of a severity factor (SF). The SF is determined from a developed health effect classification scheme. This scheme is a key element of the SAMOE approach, and differentiates the SAMOE approach from the traditional MOE, or MOE related concepts.

A semi-quantitative model for describing the uncertainty in the SAMOE estimate has also been developed. This method involves determining the level and direction of uncertainties associated with each of the parameters of the SAMOE. Whenever possible data driven input are used in this model, and if data is not available semi-quantitative standards are used instead. The overall uncertainty in the SAMOE is in addition to the point estimate accounted for in the risk classification approach discussed below.

Using a risk classification approach the SAMOE estimate is categorized in terms of health concern levels. The approach for risk classification currently consists of five Risk Classes. The main purpose of the risk classification, and the underlying SAMOE metric, is to describe chemical risks on a comparative scale. The NFA may further develop the risk classification approach regarding statements about the level of health concern that is associated with each Risk Class.

In the interim, the Risk Thermometer is considered not to be fundamentally more protective/conservative than the traditional risk assessment approach. It is regarded that exposures (at population level) that are in the range of a traditional health-based guidance value, or similar, would most likely classify in Risk Class 3 (low-to-moderate concern), which represents the midpoint of the risk classification scale. Exposures in Risk Class 3 may depending on the particular situation require

application of risk management measures, including dietary advice or regulatory initiatives, and collection of more information to fill data gaps. From a risk perspective, the application of such measures is more likely to be relevant in the case of exposures categorizing in Risk Class 4 and 5, while it seems not likely to be needed in the case of exposures categorizing in Risk Class 1 and 2.

There are challenges associated with the present as well as future approaches for comparing food related risks. However, the use of such methodology is regarded as an improvement. For example, it increases the transparency by which the severity of effect influences statements regarding health concerns associated with chemical exposures. In general, the area of chemical risk assessment is regarded to benefit from the introduction of approaches that forces the interpretation of exposures or risks in a greater context. Public interests concerning potential health risks associated with food consumption may benefit from such developments, as well as the health agencies that need to prioritize the use of their resources with respect to risk related questions.

Sammanfattning

Livsmedelsverket har utvecklat ett verktyg för att förtydliga och göra det lättare att jämföra slutsatserna av myndighetens riskvärderingar för olika typer av kemiska ämnen som finns i maten. Det huvudsakliga syftet är att kunna jämföra olika risker på en gemensam skala.

Metodiken bakom verktyget, som kallas Risktermometern, utvecklar riskvärderingsområdet och syftar även till att ge Livsmedelverket bättre metoder för att prioritera verksamheten efter hur stor risken med ett ämne är. Genom att lättare kunna jämföra risker på ett enhetligt och systematiskt sätt kan arbetet koncentreras på de kemiska ämnen som verkligen innebär en risk för hälsan.

Den stora skillnaden mot det traditionella arbetssätt som används vid riskvärdering i dag är att verktyget också tar hänsyn till hur allvarlig hälsoeffekten för ämnet är. Verktyget beräknar bland annat ett mått på risk som kallas ”severity-adjusted margin of exposure” (SAMOE) och detta görs för varje enskilt ämne.

Traditionellt utförs riskvärdering av kemiska ämnen genom en jämförelse av hur mycket befolkningen exponeras för en kemisk substans och den exponering som skulle kunna innebära hälsorisker om den överskrids (ämnets hälsobaserade referensvärde). För de flesta kemiska ämnen räcker det om det finns en viss säkerhetsmarginal mellan uppskattad exponering och det hälsobaserade referensvärdet. När det gäller en del cancerframkallande ämnen är dock bedömningen att det krävs en mycket stor säkerhetsmarginal.

Den utvecklade SAMOE-metoden skiljer sig från det traditionella arbetssättet genom att det för varje enskilt ämne görs en bedömning om vad som utgör en acceptabel säkerhetsmarginal mellan uppskattad exponering och det hälsobaserade referensvärdet.

Hur stor denna marginal behöver vara beror på vilken typ av hälsoeffekt ämnet kan orsaka, det vill säga ju allvarligare hälsoeffekten bedöms vara desto större säkerhetsmarginal används i metoden. Det krävs till exempel större marginal om ett ämne kan orsaka nervskador än om det orsakar övergående illamående. För att kunna bedöma olika hälsoeffekters allvarlighet har Livsmedelsverket utvecklat ett system för klassificering av hälsoeffekter.

Beräknade SAMOE-värden kategoriseras i fem riskklasser. För närvarande bedömer Livsmedelsverket att riskklass ≤ 2 innebär låga till mycket låga risker. Definitionen av respektive riskklass utifrån den hälsomässiga betydelsen baseras på många faktorer och kan komma att revideras.

Att använda Risktermometern innebär utmaningar eftersom allvarligheten av olika hälsoeffekter måste bedömas kvantitativt, det vill säga i siffror. Allvarligheten beaktas i dag inte inom internationell praxis på området. Livsmedelsverket menar att en kvantitativ värdering innebär en förbättring eftersom tydligheten då ökar kring hur hälsoeffektens allvarlighet vägts in.

I nuläget kan Risktermometern användas för att jämföra långsiktiga kemiska risker i samband med konsumtion av livsmedel. Den kan till exempel användas för miljögifter, metaller, bekämpningsmedel och tillsatser. I framtiden kan Risktermometern komma att utvecklas för att även kunna klassificera akuta kemiska risker, det vill säga exponeringen vid ett specifikt tillfälle, samt mikrobiologiska risker i samband med konsumtion av livsmedel.

Risktermometern består av fyra delar: 1) en ny riskvärderingsmetod, 2) en metod för att bedöma osäkerheten i resultatet, 3) en metod för klassificering av resultatet, och 4) en grafik som visar resultatet.

Denna rapport avser metodiken bakom Risktermometern (del 1, 2 och 3). Grafiken (del 4) som illustrerar resultaten kommer att utvecklas i ett senare skede för att på ett enkelt sätt kommunicera hur stor risken bedöms vara med olika ämnen i maten. Syftet är att underlätta för konsumenter och media att förstå och förhålla sig till risker med olika ämnen.

1 Objective and mandate

The objective of this project has been to develop a tool called the “Risk Thermometer” that may be used for comparison of chemical risks associated with food consumption. The Risk Thermometer aims to be an integrated part of today’s risk assessment, risk management, and risk communication workflow at the Swedish National Food Agency (NFA), and thus bridge the three elements of risk analysis. The Risk Thermometer provides the NFA with a new approach for priority-setting, and contributes for example to the further development of a risk-based food control. The Risk Thermometer also aims to communicate levels of risks to consumers, the media, and other stakeholders, and it is anticipated that it will clarify the results of quantitative risk assessments performed by the NFA.

The Director General at the NFA requested the development of a Risk Thermometer. The core project group has consisted of six members, providing expertise in the areas of risk assessment, toxicology, microbiology, nutrition, risk management, and risk communication. A steering group has also been attached to the project consisting of the heads of the departments directly involved in the project: the Department of Risk-Benefit Assessment, the Department of Advice and Emergency Preparedness, and the Department of Communications.

A public consultation on the draft report on the Risk Thermometer was held between 2014-12-17 and 2015-02-28. Both national and international organizations representing the public sector as well as the industry responded to the consultation. Specifically, comments were received from:

- The EFSA Scientific Committee
- The Finnish Food Safety Authority
- The Swedish Chemicals Agency
- The UK Food Standards Agency
- Nestlé
- The Swedish Food Federation
- Professor Robert Nilsson
- Svensk Dagligvaruhandel

NFA responses to all comments provided can be found in the “Report on Public Consultation” (NFA 2015).

2 Introduction

The Risk Thermometer developed in this project consists of four parts:

1) A severity-adjusted margin of exposure (SAMOE) approach, which is an extension of the current framework for chemical risk characterization that indirectly accounts for the probability of occurrence (or change in the response) of a health effect as well as the severity of the health effect. It is described in detail in section 3.
2) A model that describes the uncertainty in the SAMOE. It is described in detail in section 4.
3) A risk classification approach that categorizes SAMOE values in terms of health concern levels. It is described in detail in section 5.
4) A graphical illustration of the results.

This report is concerned with the presentation of the underlying elements of the Risk Thermometer, i.e., parts 1, 2, and 3, serving as its scientific and value-based foundation. The graphical front end of the tool (part 4) will be further developed. However, some examples of illustrations are included in section 6.

By choice the Risk Thermometer is based on both scientific considerations (risk assessment) and value-based considerations (risk management):

- Scientific considerations (risk assessment): the SAMOE approach (parts 1 and 2) except certain aspects of the severity classification of health effects (see Table 3).
- Value-based considerations (risk management or the borderline between risk assessment and risk management): certain aspect of the severity classification of health effects (see Table 3), and the risk classification approach (part 3).

The Risk Thermometer aims to bridge the three elements of risk analysis (risk assessment, risk management, and risk communication). The approach is, however, in line with the important principle of an operational separation between risk assessment and risk management, i.e., since the set of default value-based severity factors are transparently defined prior to the assessment (see Table 3). For example, this is similar to the application of default adjustment factors for inter- and intra-species differences in susceptibility.

The Federal Institute for Risk Assessment (BfR) has developed a risk profile that graphically summarizes the results of BfR opinions (BfR 2014). The BfR was consulted during this project since the risk profile was considered a valuable point of departure. The NFA Risk Thermometer differs from the BfR risk profile, main-

ly as parameters related to 1) the probability of occurrence (or change in the response) of a health effect, and 2) the severity of the health effect, are combined into a single variable in the NFA approach. This reduces the number of dimensions, and enables direct comparison between different food related risks which was one of the main purposes of the NFA tool.

The present version of the Risk Thermometer applies to comparison of chemical risks associated with chronic exposure via food (i.e., not acute effects). It may for example be used to assess and compare such exposures to environmental contaminants, pesticides, food additives, chemicals used in food contact materials, and minerals/nutrients.

To satisfy the objectives of the Risk Thermometer (see objective in the report) a framework for comparative risk characterization has been developed that efficiently can be integrated in today's risk assessment, risk management, and risk communication workflow at the Swedish National Food Agency (NFA). It is regarded that such a practical framework needs to be based on current risk assessment methodology, including data requirements and inputs, to a high extent. Because of this a brief introduction to current practice in the area of quantitative risk assessment of chemicals is given below.

2.1 Risk assessment of chemicals

According to the World Health Organization, the process of health risk assessment of chemicals in food is divided into four steps (WHO/IPCS 2009); hazard identification, hazard characterization (or dose response assessment), exposure assessment, and risk characterization. *Hazard identification* is the identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)-population. *Hazard characterization* involves assessment of the relationship between the dose of a chemical agent and the biological effects that are produced. A reference point (RP), also denoted point of departure (POD), is typically determined from this dose-response assessment. In the case of non-genotoxic chemicals the RP is a starting point for establishment of health-based guidance values (HBGV). *Exposure assessment* involves estimating the degree to which the human population is exposed to a chemical. Finally, *risk characterization* is defined as the qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)-population, under defined exposure conditions (WHO/IPCS 2004).

The WHO definitions are similar to those given in the Codex principles of risk analysis. It can, however, been noted that the element of "severity" is also part of the risk characterization according to Codex (FAO/WHO 2008): "The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment". The severity of a health effect is also an element of the methodology behind the Risk Thermometer described in this report.

In today's practice risk characterization typically includes assessing the significance of the estimated exposure by comparing it to the RP or the HBGV. Based on such analysis it may be concluded whether or not a given population potentially is at risk. The term "risk assessment" carries the notion that it involves the computation of the actual probability of occurrence of some health effect, which is rarely the case for chemicals. In line with current terminology, however, the term risk assessment/characterization will be used throughout this report.

Risk assessment has by tradition been performed differently whether the chemical is non-genotoxic or a genotoxic carcinogen. This relates to the assumption of the occurrence of exposure thresholds for non-genotoxic effects, and the absence of such thresholds in the case of genotoxic effects. In either case, however, a RP is typically derived as part of the hazard characterization. The RP is a quantity that is estimated from the critical animal toxicity study/studies or human epidemiological study/studies. The derivation of the RP from such data is performed using dose-response modeling approaches, or more traditionally, in the case of non-genotoxic effects, by using the no-observed-adverse-effect level (NOAEL) (Figure 1). Dose-response modeling, specifically the benchmark dose (BMD) approach, is general-

ly regarded as the method of choice for derivation of the RP by many international health organizations (EFSA 2009a; Davis et al. 2011). The introduction of the BMD approach has increased comparability between risk assessment approaches for non-cancer and cancer agents. As a result, integrated approaches to non-cancer and cancer risk assessment have been suggested [Gaylor et al. 1999; National Research Council (NCR) 2009]. Currently, a single approach (the BMD approach) is generally recommended for estimating the RP, but differences exist in terms of how to proceed after the derivation of the RP, depending on whether the agent is non-genotoxic or a genotoxic carcinogen [European Food Safety Authority (EFSA) 2005, 2009a; U.S. Environmental Protection Agency (EPA) 2005].

Non-genotoxic chemicals

When the assessment is based on a non-genotoxic health outcome characterization of the risk is generally performed by comparing the estimated exposure to a chemical with its HBGV, like the tolerable daily intake (TDI) or the acceptable daily intake (ADI). A tolerable intake is the estimated maximum amount of an agent, expressed on a body mass basis, to which each individual in a population may be exposed over a specified time period (i.e., per day, per week, or per month) without appreciable risk. The term "tolerable intake" is used for agents that are not deliberately added to the environment (e.g. environmental contaminants), while the term "acceptable intake", which has the same interpretation, is typically used for food additives and pesticides (WHO/IPCS 2004). In the U.S. the terms reference dose (RfD) and reference concentration (RfC) are used instead of "tolerable" or "acceptable" intake. Although the exact formulation of the TDI/ADI (WHO/IPCS 2004) differs to some extent from that for the RfD/RfC (EPA 2014), these quantities are derived in essentially the same manner, and can be interpreted similarly. The HBGV is established by the application of adjustment factors to the RP. These types of factors may also be denoted uncertainty factors, assessment factors, or safety factors. The general term, adjustment factors (AFs) will be used throughout this report.

$$HBGV = \frac{RP}{AFs}$$

The AFs account for inter- and intra-species differences in susceptibility. In case the RP is derived from animal toxicity data the default overall AF is 100 (10 × 10); it allows for a (possible) factor 10 increased susceptibility in humans compared with experimental animals ($AF_{interspecies}$), and a (possible) factor 10 difference in susceptibility between the "average" and "sensitive" human ($AF_{intraspecies}$). Renwick (1993) suggested that the default AFs of 10 could each be divided in two sub-factors, each of which could be replaced by the appropriate compound specific data. In the absence of such data the two sub-factors collapse back to the default value of 10. The suggestion by Renwick (1993) was later revised by WHO/IPCS (1994) (Table 1).

Table 1. Divison of the default AFs of 10 in toxicokinetic (TK) and toxicodynamic (TD) components.

Adjustment factor	Renwick (1993)		WHO/IPCS (1994)	
	TK	TD	TK	TD
$AF_{interspecies}$	$10^{0.6}$	$10^{0.4}$	$10^{0.6}$	$10^{0.4}$
$AF_{intraspecies}$	$10^{0.6}$	$10^{0.4}$	$10^{0.5}$	$10^{0.5}$

Additional considerations may further modify the overall AF depending on characteristics of the study/studies used for derivation of the RP, including its relevance for the human population group the HBGV applies to; e.g., accounting for the route of exposure in the critical study, the duration of the critical study, the adequacy of the database, and/or the severity of the critical health effect. According to current practice there may be a concern from a public health point of view if the estimated exposure to a non-genotoxic chemical exceeds the HBGV.

While extra AFs for the nature and/or severity of effect are not routinely used in today's risk assessments, except for the case of genotoxic cancer (see the section below), the possibility to use such factors is often mentioned in risk assessment guidelines. EFSA regards that such a factor may be considered on a case by case basis (EFSA 2012). The WHO drinking water guidelines suggests factors of 1 - 10 for the nature and severity of effect; a factor > 1 may e.g., be used for irreversible effects, malformation in fetuses, or if the critical endpoint is directly related to possible carcinogenicity (WHO 2011). WHO/IPCS (2009) regards that an extra AF may be used for establishment of an acute reference dose if the toxicological effect is irreversible or particularly severe. ECHA (2012) also generally discuss that the severity of effect can impact on the overall AF. As described in section 3, the approach for comparative risk characterization presented in this report involves the systematic use of an AF for the severity of effect. The introduction of the element of severity is regarded to be necessary for comparative assessment across chemicals and health effects, which is the main focus of the Risk Thermometer.

Genotoxic carcinogens

JECFA and EFSA have recommended a margin of exposure (MOE) approach for compounds that are both genotoxic and carcinogenic. The MOE is defined as,

$$MOE = \frac{RP}{exposure}$$

The MOE describes the margin between the estimated exposure to a chemical and the RP. This approach is similar, in principal, to the approach used for risk charac-

terization of non-genotoxic chemicals except that the RP, rather than the HBGV, is used as the exposure reference. EFSA and the WHO regarded that the MOE, for example, had the potential to help risk managers to distinguish between large, intermediate, and low health concerns, and thus provide guidance for setting priorities for risk management actions (Barlow et al. 2006). The EFSA Scientific Committee was of the view that in general a MOE of 10,000 or higher "would be of low concern from a public health point of view and might reasonably be considered as a low priority for risk management actions" (EFSA 2005). EFSA associates this statement to the case of an RP derived from animal toxicity data that corresponds to the $BMDL_{10}$; i.e., the lower confidence bound on the dose corresponding to a 10 % increase in quantal response (incidence) over background estimated using the BMD approach. EFSA further states that a MOE of 10,000 may not be sufficient under circumstances where there are greater uncertainties, for example if the RP is based on a poor animal database. The margin of 10,000 is based on the default AF of 100 multiplied by an additional factor of 100 which is specific for compounds that are both genotoxic and carcinogenic. The additional factor of 100 is intended to cover, 1) inter-individual human variability in cell cycle control and DNA repair, which influences the carcinogenic process, and 2) uncertainties regarding the dose effect relationship below the RP [e.g., the dose below which cancer incidence is not increased is unknown] (EFSA 2005).

The U.S. Environmental Protection Agency's (EPA's) cancer risk assessment guidelines differ from the recommendation by EFSA and JECFA. The EPA recommends low-dose linear extrapolation when 1) there are data to indicate that the dose-response curve has a linear component below the RP, or 2) as a default for a tumor site where the mode of action is not established (EPA 2005). For linear extrapolation, a line should be drawn from the RP to the origin, corrected for background (Figure 2). This implies a proportional (linear) relationship between dose and risk at low doses. Linear extrapolation permits derivation of upper-bound estimates of risk at exposure levels of interest, as well as estimation of *risk-specific doses* associated with target (upper-bound) risk levels. The typical EPA target range for risk management is a 1/1,000,000 to a 1/10,000 increased lifetime risk (EPA 2005). The MOE is also cited in the EPA guidelines, but is regarded as a quantity that provides an indication of the extent of extrapolation of risk estimates from the observed data to the exposure levels of interest (EPA 2005).

It may be noted that low-dose linear extrapolation using the $BMDL_{10}$ as a starting point for estimating the dose, *d*, corresponding to a target risk of 1/100,000, consistent with EPA guidelines, implies that the ratio (MOE) between the RP ($BMDL_{10}$) and the estimated dose, *d*, will be 10,000, consistent with the EFSA statement on an acceptable MOE. Thus, while the EPA and the EFSA guidelines differ in principle they may coincide in practice with respect to what is considered to constitute a sufficient level of protection.

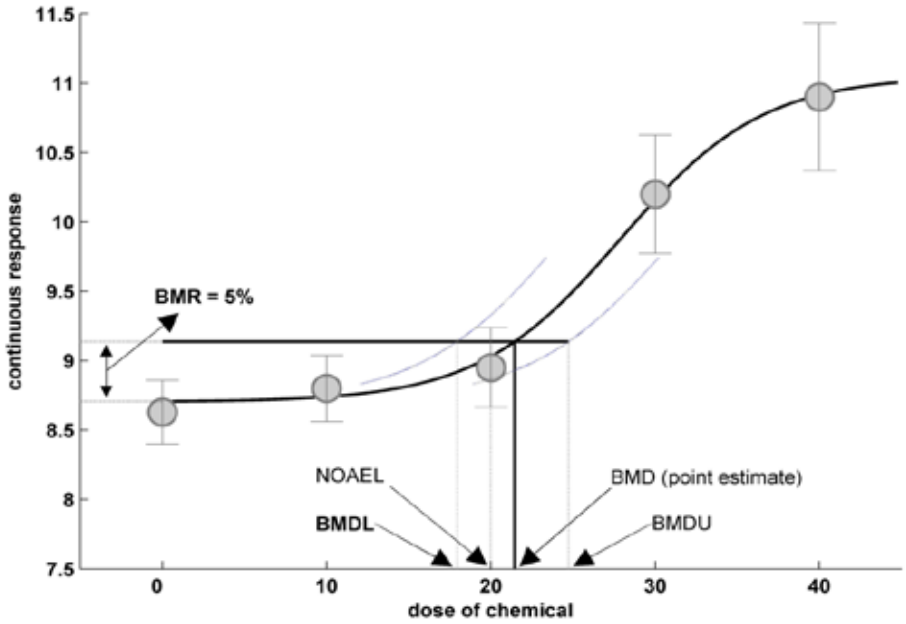


Figure 1: **Conceptual illustration of RP derivation**. The RP is typically derived from the critical toxicity study as either the no-observed-adverse effect level (NOAEL) or the lower confidence limit on the benchmark dose (the BMDL). The solid curve is a dose-response model that has been fitted to the mean responses observed at five experimental dose levels (including control) describing a continuous health outcome (animal data).

The NOAEL approach: The NOAEL is the highest experimental dose level where effects were not detected, using statistical tests and expert opinion to compare each treatment level with the control group. In this example, the NOAEL corresponds to an experimental dose of 20. The experimental dose above the NOAEL is called the lowest-observed-adverse effect level (LOAEL), i.e., a dose of 30 in this example.

The benchmark dose (BMD) approach: The BMD is defined as a dose corresponding to a low but measurable change in response, denoted the "benchmark response" (BMR). For continuous health effects, EFSA (2009a) recommends that the BMD by default is defined as the dose corresponding to a BMR of 5 % (expressed as a percent change in the mean response relative to background) consistent with this illustration. Several suggestions for how to define the BMD for continuous data have, however, been presented in the scientific literature (e.g., Sand et al. 2008). Continuous data is typically evaluated in terms of the mean response as a function of dose. Dose-response data may also be of quantal nature, describing the presence or absence of a health effect. Quantal data often represent severe lesions like cancer or malformation incidences, and EFSA (2009a) recommends that the BMD by default is defined as the dose corresponding to a BMR of 10 % (expressed as extra risk) for such data. To account for statistical uncertainties the lower confidence bound (BMDL), rather than the point estimate (BMD), is used as the RP. It has been suggested that the BMR should ideally reflect an effect size that is "acceptable" from a biological/toxicological point of view. While this is conceptually reasonable, there is presently no consensus on such BMRs for most health effects. Currently, the BMR may be considered to be set as low as possible without having to estimate the BMD by extrapolation outside the range of the data, such that it would heavily depend on the chosen model (EFSA 2009a). For experimental data, the BMR is typically set to 5 or 10 % while BMRs as low as 1 % has been applied in human studies.

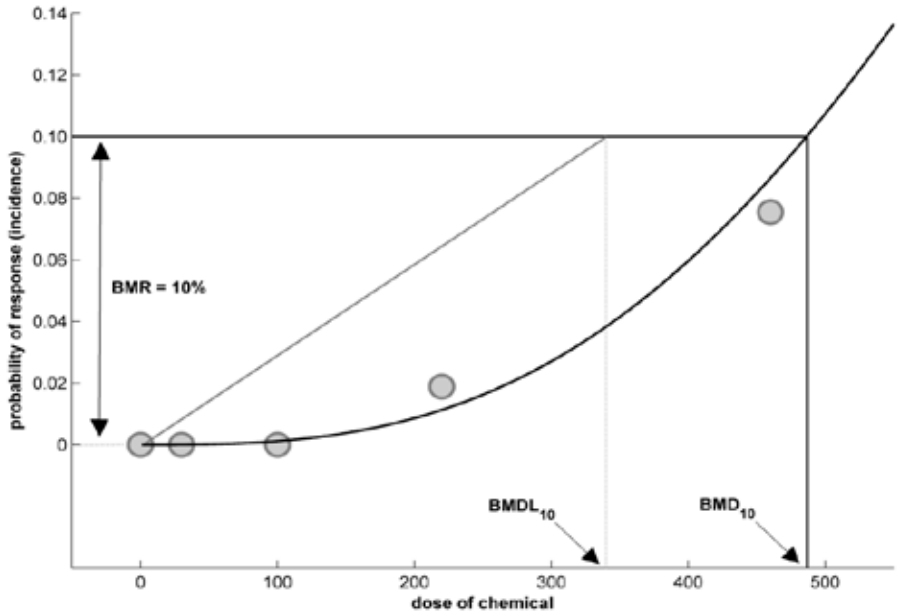


Figure 2: Conceptual illustration of low-dose linear extrapolation. The example shows a dose-response model (solid curve) fitted to data (circles) describing the incidence of a quantal health effect observed in experimental animals. Low-dose linear extrapolation is performed by drawing a straight line from the RP, in this case represented by the $BMDL_{10}$ to the background response as determined by the solid curve. Estimates of risk according to the straight line, drawn between the RP and the background, may be derived at exposure levels of interest. Similarly, estimation of doses associated with target risk levels may be also be performed; the typical EPA target range for risk management is a 1/1,000,000 to a 1/10,000 increased lifetime risk (EPA 2005). Low-dose linear extrapolation is performed since it may be unreliable to use the fitted dose-response model for computing risk estimates associated with very low doses, since such estimates may be highly dependent on the choice of dose-response model. Estimates derived by low-dose linear extrapolation are generally regarded as *upper-bound* estimates of risk. The "*true*" risk associated with a certain exposure level is likely not to be higher than the estimate from the linear extrapolation approach, but the "*true*" risk may on the other hand be lower than the derived upper bound estimate, possibly even zero. This holds for all dose-response curves for which the slope between zero and the RP is linear or increases with increasing dose. For such curves, the linear approach becomes less conservative as the BMR associated with the RP decreases: the slope of the linear model decreases with decreasing BMR which implies that the dose corresponding to a given target risk will increase, and conversely, the risk associated with a given dose will decrease. Linear extrapolation can underestimate the risk in case the curve is non-linear in the other direction; i.e., if the slope between zero and the RP decreases with increasing dose. Observe that the BMDL for quantal data is generally expressed in terms of extra risk: BMR = [p(BMD) - p(0)] / [1 - p(0)] = [0.10 - 0] / [1 - 0] = 0.10. Since the estimate of the background response, p(0), is zero in this example a 10 % extra risk equals a 10 % additional risk: BMR = p(BMD) - p(0) = 0.10 - 0 = 0.10. If p(0) is close to zero the additional risk definition approximates to the extra risk definition.

3 The SAMOE approach

As described previously, the current approach for risk characterization of chemicals is in principle based on the margin of exposure (MOE) or MOE related concepts, where the estimated exposure to a chemical in a target population is compared (in one way or another) to an exposure reference level, i.e., either a HBGV (for non-genotoxic effects/chemicals) or a RP (for genotoxic carcinogens). The EPA cancer risk assessment guidelines recommend low-dose linear extrapolation for certain substances, but this approach indirectly corresponds to a MOE approach. Thus, for chemicals the risk is generally described by a MOE. However, while the MOE indirectly relates to the probability of occurrence (or change in the response) of a health effect the severity of the health effect is generally not accounted for by this metric. “Probability” (or similar) and “severity” are both important elements of the risk concept, which e.g., is supported by the FAO/WHO (2008) definition of risk characterization. This consideration is of particular importance in the context of the Risk Thermometer since this concept involves comparative risk characterization across chemicals and health effects in contrast to applications of the traditional MOE approach.

To satisfy requirements associated with the Risk Thermometer a severity-adjusted margin of exposure (SAMOE) approach has been developed. This approach penalizes the traditional MOE depending on the severity of the critical health effect used as basis for risk assessment. This is achieved by the systematic application of a severity factor (SF). The SAMOE is regarded as a measure that may be used as a basis for comparing the exposure situation across chemicals like environmental contaminants, pesticides, food additives, chemicals used in food contact materials, and minerals/nutrients. The derivation of the SAMOE involves three basic steps.

I. A population-adjusted reference point (PARP) is derived by the application of AFs to the RP (equations 1-3).
II. A severity-adjusted reference point (SARP) is derived by the application of a severity factor (SF) to the PARP (equations 4-5, Table 3).
III. The SAMOE is defined as the ratio between the SARP and the estimated exposure to a chemical in the target population (equation 6).

The SAMOE approach is based on several considerations. The rationale behind this method is discussed in more detail in Text box 1. Also, the link between the SAMOE and the risk classification approach (see section 5) at the level of the Risk Thermometer is visualized in Figure 3. The different steps of the SAMOE approach are described below.

The population-adjusted reference point, PARP, is derived as,

$$PARP = \frac{RP}{AF_{interspecies} \times AF_{intraspecies}}, \quad (1)$$

$$AF_{interspecies} = AF_{inter\text{-}TK} \times AF_{inter\text{-}TD}$$
$$AF_{intraspecies} = AF_{intra\text{-}TK} \times AF_{intra\text{-}TD} \quad (2)$$

In the current version of the SAMOE approach the RP may be a BMD, a NOAEL, or a LOAEL (Figure 1). Observe that the lower bound of the BMD (the BMDL), rather than the point estimate (BMD), is generally used for HBGV establishment. However, in the Risk Thermometer the uncertainty in the BMD (the BMDL and the BMDU) and other parameters of the SAMOE is explicitly accounted for in the uncertainty model (see section 4). The PARP is calculated by using a chemical-specific adjustment factor (CSAF) approach according to WHO/IPCS (1994). $AF_{interspecies}$ and $AF_{intraspecies}$ equal the default AF of 10, respectively, in case there is no chemical-specific information available. The AFs are further described in Table 2.

The PARP is considered to be a form of standardized HBGV. The term "PARP" rather than "HBGV" is used since 1) a HBGV is traditionally not derived for genotoxic carcinogens, and 2) the overall AF applied to the RP for establishment of a HBGV in the case of non-genotoxic chemicals may be assessment-specific resulting in that different health organizations may arrive at different HBGVs for the same chemical even though the RP is identical or similar, e.g., the case of methyl mercury (NCR 2000; JECFA 2003). While it is reasonable to allow a high degree of freedom in the AF selection in the case of chemical-specific assessments, a comparative risk assessment framework may require higher standardization in this respect.

An RP corresponding to a standard BMR level of 10 % (BMR = 0.10) expressed as extra risk, additional risk, relative effect, absolute effect, or extra effect is used in the current approach (e.g., see Sand et al. 2008 for a review of BMR definitions). The BMR level associated with the RP may, however, differ between assessments; for example the BMR level has sometimes been set lower for epidemiological data compared with experimental data describing the same health effect. In addition, the RP may be a NOAEL or a LOAEL. To account for diversity in RPs an additional AF is applied if 1) the impact of a BMR level set to a value different from 10 % is regarded to be significant, e.g. a BMR = 0.01, or 2) if the RP is based on a LOAEL.

$$PARP_{10} = \frac{PARP}{AF_{BMR}}, \quad (3)$$

In equation (3), AF_{BMR} = 3 is used as a default if the RP is a LOAEL, i.e. downward adjustment of the RP (ECHA 2012). Also, if the RP is a BMD_{01} (BMR = 0.01) a default AF_{BMR} = 1/3 is used for upward adjustment. Other values of AF_{BMR} may be used on a case by case basis, and AF_{BMR} is set to 1 in case of a BMD_{10} or a NOAEL. In Text box 1 more details behind this AF application is provided.

The SAMOE approach is based on the general consideration that the adequate safety margin between the $PARP_{10}$ and the estimated exposure to a chemical depends on the severity of the critical health effect used for RP derivation. To this end, a severity-adjusted reference point (SARP) is derived by the application of a severity factor (SF) to the $PARP_{10}$. The SARP is the primary exposure reference level in the SAMOE approach. In the risk classification approach (section 5) this SARP is denoted $SARP_{low}$ where it represents one of several reference levels that define borders between the Risk Classes.

$$SARP = \frac{PARP_{10}}{SF}, \quad (4)$$

$$SF = 10^{x} \quad (5)$$

The *x* variable in equation (5) is determined according to a developed health effect classification scheme (Table 3), and the resulting SF may currently assume default values of 1, 3.16, 10, 31.6, and 100. SFs of 1, 10, and 100 are used for *mild*, *moderate*, and *severe* toxicity outcomes, respectively. Application of the SF is regarded to result in a SARP below which exposures may be of low concern (see section 5). The severity classification and SF determination currently involves both science-based (risk assessment) and value-based (risk management) considerations. It is described in Table 3, where the interpretation of the SF application is also discussed in further detail.

The severity-adjusted margin of exposure, SAMOE, is calculated as,

$$SAMOE = \frac{SARP}{E} \quad (6)$$

where SARP is the severity-adjusted reference point defined in equation (4). *E* is the estimated chronic (long-term) exposure to a chemical in the target population; it may be a central estimate like median or mean, or a given percentile of exposure (e.g., the upper 95th percentile). *E* may be based on an exposure assessment that combines consumption data and concentration data for a particular food product or all relevant foods. Alternatively, *E* may be estimated from biomonitoring data in the target population.

A SAMOE > 1 implies that the exposure is below the SARP, i.e., the margin between $PARP_{10}$ (the HBGV equivalent) and the exposure is larger than the SF. This may be indicative of a low health concern. Observe that the SAMOE applies to

the target population under investigation. Thus, aspects like population size are not part of the SAMOE approach.

A description of how the SAMOE approach as well the risk classification approach (section 5) compares to the traditional approach for risk characterization is given in Text box 3. In summary, by combining equations 1 - 6 the overall equation for the SAMOE is

$$SAMOE = \frac{RP}{AF} \times \frac{1}{AF_{BMR}} \times \frac{1}{SF} \times \frac{1}{E}, \quad (7)$$

where AF is the overall adjustment factor for inter- and intra-species differences in susceptibility.

Also, the SAMOE may be generalized to the case of cumulative exposure as written below

$$SAMOE = \frac{RP_{index}}{AF} \times \frac{1}{AF_{BMR}} \times \frac{1}{SF} \times \frac{1}{\sum_{i=1}^{g}(E_i \times RPF_i)}, \quad (8)$$

where RP_{index} is the RP associated with the index chemical for which the overall AF, and BMR applies to; where g is the number of chemicals; where E_i is the estimated exposure associated with the i'th chemical; and where RPF_i is the relative potency factor associated with the i'th chemical in relation to the index chemical. This assumes that chemicals in the mixture act by dose addition (additively). Potentials for further extensions of the SAMOE approach are discussed in section 7.

Text box 1. Rationale and considerations behind the SAMOE approach

To satisfy the objectives of the Risk Thermometer a framework for comparative risk characterization has been developed that efficiently can be integrated in today's risk assessment, risk management, and risk communication workflow at the Swedish National Food Agency (NFA). Such a practical framework needs to be based on current methodology and risk assessment practice, including data requirements as well as the use of default values (e.g., adjustment factors, AFs), to a high extent. These considerations have been important for the selection and design of the severity-adjusted margin of exposure (SAMOE) approach.

As discussed in the introduction (section 2.1) the term "risk assessment" carries the notion that it involves the computation of the probability of occurrence of some health effect at a given exposure. However, this is rarely the case for chemicals, and margin of exposure (MOE) or MOE related concept are instead used. While the MOE indirectly relates to the probability of occurrence, or change in the (mean) response, of a health effect, the severity of the health effect is generally not accounted for by this metric. Both "probability" (or similar) and "severity" are regarded to be important elements of the risk concept, as e.g., supported by the FAO/WHO (2008) definition of risk characterization. This consideration is of particular relevance herein since the objective of the Risk Thermometer involves comparative risk characterization across different chemicals and health effects in contrast to applications of the traditional MOE approach (traditional quantitative risk characterization is performed without reference to how the assessment for a given chemical stands with respect to the assessment of another chemical).

The SAMOE approach satisfies requirements associated with Risk Thermometer by penalizing the traditional MOE value depending on the severity of the critical health effect used as basis for risk assessment. This is achieved by the systematic application of a severity factor (SF). The SF is determined from a developed health effect classification scheme. This scheme represents the central element of the SAMOE approach, and the systematic use of a SF differentiates the SAMOE approach from more traditional margin of exposure related concepts. The scheme is discussed in detail in Table 3. Some additional considerations are noted below:

- The change in risk/effect for a given health effect that would be of low concern (the "acceptable" change in risk/effect) relates to the severity of that risk/effect. Conceptually, this is consistent with stating that that the MOE which is of low concern (the SF) depends on the severity of the health effect. The change in risk/effect at the severity-adjusted reference point (SARP) indirectly becomes lower for more severe health effects due to the application of a larger SF.
- The level of risk/effect reduction achieved for given SF application depends on the shape of the dose-response curve. However, this issue is also relevant for a traditional MOE; the level of protection associated with a given MOE, in terms of change in risk/effect, depends on the shape of the curve.
- It may be discussed how large the SFs in fact should be. Currently, default values have been suggested that may be further modified (see Table 3). However, it should be noted that the general use of default values (e.g. AFs) are currently an important element in today's risk assessment practice.

<u>Thresholds</u>

Thresholds are traditionally assumed for non-genotoxic effects. Observe that the standard response associated with the RP in the SAMOE approach is 10 %, and the NOAEL also corresponds to a change in risk/effect, which may be 5 to 10 % at the median (EFSA 2009a; Sand et al. 2011). It is thus regarded that the threshold is somewhere below a default the health-based guidance value, HBGV = RP/AFs (see equations 1 - 2), where AF application relates to population-adjustments only, and does not describe risk/effect reduction in the RP. As noted by others, a threshold cannot readily be quantified (Slob, 2007). Even if the SF used in the SAMOE approach would push the SARP below the threshold the NFA regards it still reasonable to require a higher safety margin in case of a more severe health effect (for purposes related to quantitative comparisons across

Text box 1. Rationale and considerations behind the SAMOE approach

health effects). For example, if the RP is based on a severe health effect increases in the exposure above the threshold (resulting in effect/risk changes) would have a more significant impact compared to if the RP was based on a "mild" health effect. In line with this it is also considered that two *default* HBGVs do not necessarily provide the *same* level of protection if they are based on health effects that differ in severity.

The SAMOE approach in relation to other suggestions for how to account for severity

In the field of benchmark dose analysis it has been discussed that the RP may be defined as corresponding to a non-adverse change in response with respect to the critical health effect (EFSA 2009a). In this case, the severity of effect is accounted for by the BMR level itself, e.g., making RPs more applicable in a comparative risk assessment setting and not requiring the application of SFs. In fact, using RPs based on so called "critical effect sizes" would imply a form of SAMOE approach rather than a MOE approach, since the concept of severity would then be a built in function of the RP. For continuous data, a BMR level in the observable region of response may be non-adverse, representing a low health impact (e.g., Slob 2002), but there is generally no consensus on such BMR levels for most health effects. Also, for some endpoint the "non-adverse" effect/risk level may be below the limit of detection (e.g. cancer risk) reducing the general applicability of this approach. Moreover, the National Food Agency (NFA) will need to rely on RPs established by international health agencies to a high extent, and in such assessments the RP has generally not been determined, specifically, as corresponding to a non-adverse BMR level. Currently, the BMR may be considered to be set as low as possible without having to estimate the BMD by extrapolation outside the range of the data (EFSA 2009a). Therefore, as a starting point it was regarded more reasonable/practical to use an SF approach involving the categorization of health effects in terms of severity at the level of the overall endpoint (Table 3) rather than determining and categorizing levels of severity by levels of BMR values.

Detailed considerations

Due to the application of SFs it is regarded that a standardized RP (an RP that is consistently defined e.g., as corresponding to a given response) best fits the SAMOE approach. The current approach for RP derivation, often implying the selection of a BMR = 0.1, meets this requirement to some extent. An extra risk of 0.10 is the default BMR level recommended for quantal data (EFSA 2009a; Davis et al. 2011). For continuous data, EFSA (2009a) recommends a relative BMR of 5 % as a default (Figure 1). In practice, however, a relative BMR of 10 % appears to have been used most frequently for continuous data [data not shown; overview of data from the Integrated Risk Information System at: http://www.epa.gov/iris/]. Some specific situations are addressed in the bullets below:

- If the RP is based on a LOAEL downward adjustment by a factor 3 (AF_{BMR} = 3 by default) is performed based on recommendations by ECHA (2010).
- If the BMR is set as low as 1 % and the BMD_{10} cannot be derived from the data/information source used as basis for RP derivation, a factor 3 (AF_{BMR} = 1/3 by default) is applied for upward adjustment.
- Other values for AF_{BMR} may be applied in the case of a LOAEL or a BMD (corresponding to a BMR different from 10 %) on a case by case basis.
- No response-adjustment is made in the case of a NOAEL.

The use of a BMD corresponding to a BMR = 0.10, and sometimes other BMDs (after response-adjustment), under various response definitions (i.e., extra risk, additional risk, relative effect, absolute effect, or extra effect), as well as NOAELs and (response-adjusted) LOAELs is a pragmatic approach reflected by the current state of art. The risk assessment area may for example develop towards a use of more standardized RP approaches in the future (see section 7), and the current approach may in this context be subject to refinement.

Table 2. Adjustment factors used for derivation of the population-adjusted reference point (PARP).

Criterion	Adjustment factor (AF)		Value[a]
RP based on human data	$AF_{inter\text{-}TK}$ and $AF_{inter\text{-}TD}$		1
RP based on animal toxicity data	$AF_{inter\text{-}TK}$	chemical-specific AF data *available*	CSAF
	$AF_{inter\text{-}TK}$	chemical-specific AF data *not available*	$10^{0.6}$
	$AF_{inter\text{-}TD}$	chemical-specific AF data *available*	CSAF
	$AF_{inter\text{-}TD}$	chemical-specific AF data *not available*	$10^{0.4}$
Target population *not more* susceptible than study population used for RP derivation	$AF_{intra\text{-}TK}$ and $AF_{intra\text{-}TD}$		1
Target population *more* susceptible than study population used for RP derivation	$AF_{intra\text{-}TK}$	chemical-specific AF data *available*	CSAF
	$AF_{intra\text{-}TK}$	chemical-specific AF data *not available*	$10^{0.5}$
	$AF_{intra\text{-}TD}$	chemical-specific AF data *available*	CSAF
	$AF_{intra\text{-}TD}$	chemical-specific AF data *not available*	$10^{0.5}$

Note: The AF approach for inter- and intraspecies differences in susceptibility is based on WHO/IPCS (1994).
$AF_{inter\text{-}TK}$ is the toxicokinetic part of $AF_{interspecies}$
$AF_{inter\text{-}TD}$ is the toxicodynamic part of $AF_{interspecies}$
$AF_{intra\text{-}TK}$ is the toxicokinetic part of $AF_{intraspecies}$
$AF_{intra\text{-}TD}$ is the toxicdynamic part of $AF_{intraspecies}$
[a] The CSAF is the chemical-specific adjustment factor.

Table 3. Health effect classification scheme where the severity factor, SF = 10^x.

Category 1			Category 2			Category 3		
1a $x = 0$ (mild)	**1b** $x = 0.5$	**1c** $x = 1$ (moderate)	**2a** $x = 0.5$	**2b** $x = 1$ (moderate)	**2c** $x = 1.5$	**3a** $x = 1$ (moderate)	**3b** $x = 1.5$	**3c** $x = 2$ (severe)
Early clinical signs of toxicity **1a)**: For example, ruffled hair or changed activity in experimental studies, or irritation (e.g., redness, salivation) of epithelial or mucosal surface in contact with chemical. **Markers of toxicity** Changes in biological parameters considered or suspected to be early precursors of adverse response or disease. **1a)**: Change in biological or bio-chemical parameter unspecifically related to Category 2 or 3 effects (e.g., hematology, red blood cells, hematocrit, plasma protein). **1b)**: Change in precursor for Category 2 effects. **1c)**: Change in precursor for Category 3 effects.			**Hepatotoxicity or nephrotoxicity** Effects on the liver or kidney. **2a)**: Change in liver/kidney enzyme/marker levels. Change in relative liver/kidney weight. **2b)**: Change in liver/kidney pathology/function. **2c)**: Manifest liver/kidney disease. Increase of cell necrosis. Severe organ dysfunction. **Neurotoxicity** Effects on the nervous system. **2a)**: Change in (mild) neurochemical or neurophysiological markers. **2b)**: Change in central or peripheral neuropathology. Change in brain weight. **2c)**: Change in behavioral or neurological/neurophysiological endpoints. Manifest disease. **Pulmonary or cardiovascular toxicity** Effects on either the lung or lung function or the heart or heart function. **2a)**: Change in clinical chemistry parameters/markers. **2b)**: Change in function (e.g., change in blood pressure, ECG rhythm). Hypertrophy or hyperplasia. **2c)**: Manifest disease, severe organ dysfunction. **Immunotoxicity** Effects on the immune system. **2a)**: Change in immune cell parameters/markers (e.g., antibody or cytokine/chemokine levels, lymphocyte numbers). **2b)**: Functional effects on the immune system (e.g., reduced antibody production, decreased NK cell activity). Sensitization. **2c)**: Reduced host resistance in experimental infection and tumor models. Allergic reactions.			**Developmental toxicity** Effects on the developing organism that may result from exposure prior to conception, during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include; death of the developing organism, structural abnormality, altered growth, and functional deficiency (EPA 1991). **3a)**: Change in offspring or-gan/body weight or size, and litter data. **3b)**: Functional deficiencies; alterations/delays in the physiological and/or biochemical competence of an organ or organ system. Mild structural variation. **3c)**: Increase in offspring malformations (teratogenicity; moderate/severe structural variation). Severe functional deficiencies. Death of developing organism. **Reproductive toxicity** Effects on the reproductive capacity of the parent generation. **3a)**: Change in biochemical markers (e.g., hormones, enzymes). Change in reproductive organ weights. **3b)**: Pathological changes in reproductive organs. Functional effects of changes in estrus cycle. Change in sperm counts, motility, or morphology. Change in duration of pregnancy. **3c**): Decreased fertility or number of fetuses.		

Table 3. Health effect classification scheme where the severity factor, SF = 10^x.

	Gastrointestinal toxicity Effects on the gastrointestinal system. **2a)**: Irritation, hyperplasia. **2b)**: Inflammation/pathology. **2c)**: Manifest disease. **General organ toxicity** **2a)**: Change in absolute/relative organ weight. Organ specific markers of toxicity (e.g., changes in thyroid hormone levels). **2b)**: Macroscopic pathology (e.g., fat accumulation, pale color). **2c)**: Microscopic pathology (e.g., necrosis, severe fatty infiltration).	**Cancer** **3a)**: Genetic toxicity *in vivo*. **3b)**: - **3c)**: Increase in cancer risk. **Highly severe and fatal systemic toxicity** **3c)**: For example, lethal neurological, cardiovascular, or autoimmune effects.

Other toxicity

x = 0, 0.5, 1, 1.5, or 2

Background

The classification scheme has been developed using the schemes discussed by Burke et al. (1996) and Owen (2002) as starting points. The scheme by Burke et al. (1996) is severity-based but has a low resolution, and the scheme by Owen (2002) is clearer in terms of health effect category definitions but is not severity-based (Hammerling et al. 2009). The current scheme allows for a higher resolution in severity than Burke et al. (1996) and the grouping of health effects introduced by Owen (2002) has been further developed. The present scheme currently consists of thirteen toxicity-specific subgroups dynamically separated in three main severity categories, Category 1, 2, and 3. In Burke et al. (1996), Category 1, 2, and 3 effects in the present scheme were regarded as "generally reversible/generally not life-shortening", "may be irreversible/may be life-shortening", and "irreversible/life-shortening". They were weighted by factors of 1, 10, and 100 (called Toxicity Severity Indices), respectively. While these factors were not specifically developed for determination of the SF in the SAMOE approach they represent previous suggestions regarding the weighting of three broad health effect categories in terms of severity. The selection of default SFs is also based on the consideration that an SF = 100 would provide a level of protection which is similar to that suggested by EFSA for compound that are both gentoxic and carcinogenic. Given a standard scenario of an RP corresponding to the $BMDL_{10}$ derived from animal data, and an overall AF = 100 for inter- and intra-species differences in susceptibility in combination with a SF = 100, would correspond to a MOE = 10,000. Gaylor et al. (1999) has also more generally suggested the use of an animal $BMDL_{10}$ in combination with a total AF of 10,000 in the case of severe irreversible adverse health effects such as carcinogenesis, mutagenesis, and teratogenesis. The upper limit of the SF (100) is also based on these scenarios.

Interpretation of the SF application

At a general level, the SAMOE approach is based on the consideration that the adequate safety margin between the population-adjusted reference point ($PARP_{10}$; equation 1 - 3) and the estimated exposure depends on the severity of the critical health effect used for RP derivation. This is a pragmatic view on the SF application, and SFs of 1, 10, and 100 are applied for *mild*, *moderate*, and *severe* toxicity outcomes, respectively, resulting in a severity-adjusted reference point (SARP, equation 4). Exposures below the SARP are effectively considered to be of low concern. In the risk classification approach (section 5) this SARP is denoted $SARP_{low}$ where it represents one of several reference levels used to defined borders between the Risk Classes.

Table 3. Health effect classification scheme where the severity factor, $SF = 10^x$.

At the SARP the change in effect/risk of the critical health effect is regarded to be significantly lower than the standard BMR = 0.10, or if the critical effect has a threshold it may even be zero. It is considered that events associated with severity levels a, b, and c within each toxicity-specific subgroup in general are dose dependent, and may also be linked to early markers of toxicity (Category 1). Thus, SF application resulting in the SARP is also regarded as extrapolation, schematically, to early events or precursors for the critical effect. Conceptually, the SF is regarded to describe the ratio between the BMD_{10} for the critical effect and the BMD_{10} for an early precursor for the critical effect (a Category 1a effect). Default values are currently used for the SF. The classification scheme may be revised in the future; the range of *x* values, and their separation, may be improved e.g., by new (mechanistic) data explaining dose-dependent chain of events within and between individual toxicity-specific subgroups. Also, the view of the SF as a BMD ratio may enable probabilistic implementation of this approach similar to that discussed for adjustment factors (e.g., van der Voet and Slob 2007; Hasegawa et al. 2010) (see also section 4).

Guidance for determining the SF

The critical health effect parameter used as basis for reference point (RP) derivation is first classified into one of the toxicity-specific subgroups (e.g., hepatotoxicity). The value of *x* in the equation for the severity factor ($SF = 10^x$) may then assume a value corresponding to any of the severity levels defined for the toxicity-specific subgroup. Generally, three severity levels (a, b, or c) of *x* can be selected. The levels a, b, and c are defined so that the SF is allowed to overlap between the three main categories. Differentiation between the main categories is thus dynamic reflecting that:

1) The nature of specific health endpoints that belong within in a given toxicity-specific subgroup (e.g., nephrotoxicity) may be quite diverse; e.g., a change in relative kidney weight ($x = 0.5$) vs. a change in kidney cell histopathology ($x = 1.0$) vs. chronic kidney disease ($x = 1.5$).

2) Even though Category 3 effects (e.g., developmental toxicity) may generally be regarded to be more severe than Category 2 effects (e.g., nephrotoxicity) at population level this may also depend on the specific endpoint.

The guidance in this Table does not cover every scenario, and the level of detail provided presently diverges between toxicity-specific subgroups. Also, classification is generally coupled to a standard BMR = 0.10 expressed as extra/additional risk or relative/absolute/extra effect. Moreover, the scheme is designed so that there are links across the categories. For example, a parameter classified as a marker of toxicity (Category 1) overlaps numerically with Category 2a or 3a effects, respectively, or may be regarded as an early precursor of such effects (Category 1a). Also, neurotoxicity may span both Category 2 and 3 effects resulting in *x* values between 0.5 and 2 (neurotoxicity, developmental neurotoxicity, and lethal neurological effects).

The case of several potential RPs/critical effects

A chemical may be able to cause various health effects. For example, it may display additional and more severe effects at doses above the critical effect. This is one basis for the SF application in the SAMOE approach. Collection of information regarding RPs for “mild”, “moderate”, and “severe” health effects may help to revise the default SFs. Also, future studies may investigate if RPs for “mild”, “moderate”, and “severe” effects, or similar, for a specific chemical and “critical pathway” directly can be used as basis for establishing exposure reference levels in a multidimensional context. This would be compound specific and data driven equivalents to $SARP_{low}$, $SARP_{mod}$, and $SARP_{high}$ that currently are derived by application of SF, SF/10, and SF/100 and define borders between the Risk Classes (see section 5 and Figure 3).

Table 3. Health effect classification scheme where the severity factor, SF = 10^x.

Presently, however, in situations when it is regarded relevant to consider several RPs and/or SFs, SAMOEs for each of these scenarios may be derived that jointly can be used as basis for risk classification (see section 5). Sometimes (additional) adjustment factors are applied within the current risk assessment practice to account for the adequacy of the database. This may for example be related to a case with several potential critical effects and RPs.

Scientific considerations (risk assessment) versus value-based considerations (risk management)
The grouping of health endpoint is toxicologically-based such that a "new endpoint" is introduced based on the toxicity it relates to (e.g., gastrointestinal toxicity). Also, it is considered that events associated with severity levels a, b, and c within each toxicity-specific subgroup in general are dose dependent, and may also be linked to early markers of toxicity (Category 1) implying chains of increasing SFs.

However, the fact that Category 3 endpoints, and markers thereof (Category 1c), are generally regarded to be more severe than Category 2 endpoints, and markers thereof (Category 1b) is a function of value-based judgment. Also, the quantitative values of the SF is based on such considerations and represents default values similar to those used in today's risk assessment practice in various respects; e.g., for animal to man extrapolation, LOAEL to NOAEL extrapolation, inadequacy of the database, and sometimes for the nature or severity of effect. The classification scheme may be revised in the future.

4 Uncertainty model

A separate model that describes the uncertainty associated with the estimated SAMOE has also been developed. The uncertainty in the SAMOE ($SAMOE_U$) is calculated as,

$$SAMOE_U = \frac{10^{RP_U}}{10^{AF_U} \times 10^{SF_U} \times 10^{E_U}} \quad (9)$$

$$AF_U = AF_{U\text{-}inter\text{-}TK} + AF_{U\text{-}inter\text{-}TD} + AF_{U\text{-}intra\text{-}TK} + AF_{U\text{-}intra\text{-}TD} + AF_{U\text{-}BMR}$$

The parameters of $SAMOE_U$ represent uncertainties associated with the parameters defining the SAMOE. Essentially, equation (9) corresponds to that for the SAMOE (see equation 7). Equation (9) describes the uncertainty in terms of a factor deviation from the SAMOE. The multiplication SAMOE × $SAMOE_U$ will translate the result at the level of the absolute scale.

In the first version of the Risk Thermometer, the parameters of $SAMOE_U$ (RP_U, E_U, AF_U, and SF_U) are assumed to be uniformly distributed. The median, lower 5th and upper 95th confidence limit of $SAMOE_U$ is derived by performing 10,000 iterations of equation 9; i.e., a value is randomly drawn from the uniform uncertainty distribution with respect to each model parameter (RP_U, AF_U, SF_U, and E_U), equation 9 is then solved, and this process is repeated 10,000 times. The selection of lower and upper bounds for the uniform uncertainty distributions is generally described below. See Text box 2 for further guidance.

RP_U: Ideally, the estimated uncertainty associated with the RP should be data driven. In this case the lower and upper bound for the uniform distribution for RP_U is set so that 10^{RP_U} corresponds to the (statistical) lower 5th and upper 95th confidence interval for the BMD, respectively. If the RP corresponds to a NOAEL or LOAEL the lower/upper bounds of the uniform distribution are based on quantitative standards (see Text box 2).

E_U: Ideally, the estimated uncertainty associated with E (the exposure) should be data driven. In this case the lower and upper bound for the uniform distribution for E_U is set so that 10^{E_U} corresponds to the lower and upper confidence limit (describing uncertainty), respectively, for the exposure quantity of interest (e.g., the median exposure). If data is not available, the lower/upper bounds of the uniform distribution are based on quantitative standards (see Text box 2).

AF_Us and SF_U: While the RP and E represent data inputs in the SAMOE approach the adjustment factors (AFs) and the severity factor (SF) represents default values. It is generally regarded that the uncertainty in the SAMOE increases with an increasing application of default values. This is currently accounted for in a semi-

quantitative manner. The uncertainty associated with a default value (AFs or SF) used in the SAMOE approach is assumed to be uniformly distributed on the log scale, and the lower/upper bounds are based on quantitative standards. The uncertainty associated with this element of the SAMOE approach will decrease with a decreasing number of default values applied, and it will reduce to zero if no default values are used (see Text box 2).

It is noted that there are suggestions in the scientific literature for how to account for uncertainties in default values, like AFs, in a probabilistic setting (e.g., Baird et al. 1996; van der Voet and Slob 2007; Hasegawa et al. 2010; Kalantari et al. 2013). According to these suggestions AFs are typically assumed to be log-normally distributed, e.g., the default AF of 10 for animal-to-man extrapolation represents an upper percentile in these distributions (i.e., not the median) resulting in a less conservative approach compared to the current practice of AF application. However, specifications of the appropriate uncertainty distributions for AFs appear to differ between suggestions. Similarly, it can be further discussed how an uncertainty distribution best can be specified for the SF. Because of this it was decided not to elaborate further on this concept in the first version of the Risk Thermometer but instead use uniform distributions (for RP_U, E_U, AF_U, and SF_U). Currently, the approach used for the default values is designed to reflect the extent of application of such values, which generally is regarded to increase the overall uncertainty in the assessment. Future versions of the Risk Thermometer may aim at defining more appropriate uncertainty distributions for all parameters of the SAMOE (see section 7).

Text box 2. Uncertainty model guidance

Uncertainty in the reference point (RP_U)

Data driven uncertainty

RP_U is assumed to be uniformly distributed. The lower and upper bound is set so that $\mathbf{10}^{RP_U}$ corresponds to the lower 5th and upper 95th confidence limit, respectively, for the BMD (the BMDL and the BMDU). If the BMD and BMDL are reported only, the uncertainty upwards is assumed to be the same as downwards in relative terms (i.e., BMD/BMDL).

Quantitative standards

RP_U is assumed to be uniformly distributed. The lower/upper bound is set to -/+ 0.2 if a point estimate of the BMD is available only, and when the RP is a NOAEL or a LOAEL. This corresponds to the uncertainty assumed for each default AF (see below). The default lower/upper bound value may be decreased or increased on a case by case basis.

Uncertainty in the exposure (E_U)

Data driven uncertainty

E_U is assumed to be uniformly distributed. The lower and upper bound is set so that $\mathbf{10}^{E_U}$ corresponds to the lower and upper confidence limit (describing uncertainty), respectively, that is associated with the exposure quantity of interest (e.g., the mean, median, or a given percentile of exposure). This may be:

1) The lower 5th and upper 95th confidence limits from probabilistic exposure assessments.
2) Results associated with lower and upper bound assumptions for concentration values below the limit of detection/quantification (LOD or LOQ).
3) The lower 5th and upper 95th confidence limits from biomonitoring data.

Quantitative standards

E_U is assumed to be uniformly distributed. The lower/upper bound is set to -/+ 0.2 if data describing uncertainties are not available. This corresponds to the uncertainty assumed for each default AF (see below). The default lower/upper bound value may be decreased or increased on a case by case basis.

Uncertainty in the assessment factors (AF_Us) and the severity factor (SF_U)

With respect to these parameters, which represent default values, the uncertainty model is designed to reflect the extent of application of such values, which generally is regarded to increase the overall uncertainty in the assessment. All AF_Us and the SF_U are assumed to be uniformly distributed.

1) For default values > 1 the lower/upper bound is set to -/+ 0.2.
2) For default values = 1 the lower/upper bound is set to -/+ 0.

A maximum of six default values > 1 may be applied; four AFs for inter- and intra-species differences in susceptibility (overall AF = 100), one AF for response adjustment, and one SF. If the uncertainty associated with six default values is assessed separately (sampling values from six uniform distributions, and performing 10,000 iterations of equation 9), the ratio between the upper 95th and lower 5th confidence limits of the overall uncertainty distribution will be close to 10 (around a factor 8-9). The quantitative standard of -/+ 0.2 units is based on this consideration. The uncertainty associated with this element of the SAMOE approach will decrease with a decreasing number of default values applied, and it will collapse to zero if no default values > 1 are used.

5 Risk classification approach

An approach for classification of risks has been designed that categorizes the SAMOE estimate in different Risk Classes that describe various levels of health concerns (Table 4). This categorization involves value-based considerations (risk management). The link between the exposure, the SAMOE approach, and the risk classification approach is visualized in Figure 3.

The classification approach currently consists of five Risk Classes. Comparison according to the SAMOE is primarily exposure related, and consequently this applies also to the risk classification. The terms “risk classification” and “Risk Class” is, however, used since the significance of an exposure in a risk context is regarded to increase as the SAMOE decreases. The main purpose of the risk classification, and the underlying SAMOE metric, is to describe chemical exposures/risks on a comparative scale. The NFA may further develop the classification scale regarding statements/descriptions about the level of health concern that is associated with each Risk Class. In the interim, however, a number of considerations have been made in this context (Table 4).

While the SARP is the primary exposure reference level in the SAMOE approach, additional reference levels are also considered at the level of the risk classification approach. As discussed in section 3 and in Table 3, application of a given SF to $PARP_{10}$ is regarded to result in a reference point (the SARP) that is associated with low health concern, schematically similar to that associated with a reference point for a mild toxicity outcome (Table 3; Category 1a for which SF = 1). This reasoning could be extended considering the structure of the health effect classification scheme where SFs for “mild”, “moderate”, and “severe” toxicity outcomes are separated by factors of 10 (Table 3). SARPs derived by the application of SF, SF/10, and SF/100 to $PARP_{10}$ (equation 4) may then, more generally, be considered to represent reference points associated with “low” ($SARP_{low}$), “moderate” ($SARP_{mod}$) and “high” ($SARP_{high}$) health concerns. This translates to SAMOEs of 1, 0.1, and 0.01, respectively, in case of exposure estimates that calibrates to the respective reference point (Table 4 and Figure 3). $SARP_{low}$, $SARP_{mod}$, and $SARP_{high}$ are used to define the borders between four of the Risk Classes, while the border between Risk Class 1 and 2 is defined pragmatically (Table 4 and Figure 3).

The uncertainty in the classification of a particular exposure in Risk Class 1, 2, 3, 4, or 5 is assessed categorically. It may be “low”, “moderate”, or “high” in the downward and/or upward direction. This assessment is based on the extent by which the uncertainty in the SAMOE spans Risk Classes below and/or above the selected Risk Class. See Table 5 for more details.

As discussed in section 2.1, additional AFs may be applied in current risk assessments to account for the adequacy of the database. This may be related to a case with several potential critical effects and RPs. In situations when it is regarded relevant to consider several RPs and/or SFs, SAMOEs for each of these scenarios may be derived that jointly can be used as basis for risk classification. Also, results from the risk classification apply to the target population under investigation, which is defined in the mandate, i.e. the risk management question. Thus, aspects of total public health burden, e.g., taking population size into account, are not explicitly included. However, results for different target populations may be derived as a basis for risk management.

As further described in Text box 3, at the level of risk classification, the Risk Thermometer is regarded not to be fundamentally more protective/conservative than the approach for traditional risk characterization. It is considered that exposures (at population level) that are in the range of a traditional health-based guidance value, or similar, would most likely classify in Risk Class 3 (low-to-moderate concern) which represents the midpoint of the risk classification scale. Exposures in Risk Class 3 may depending on the particular situation require further considerations and application of risk management measures, including dietary advice or regulatory initiatives (e.g., if the result is due to high exposures), and collection of more information to fill data gaps (e.g., if the result is due to high data uncertainties). From a risk perspective, application of such measures is more likely to be relevant in the case of exposures categorizing in Risk Class 4 and 5, while it seems not likely to be needed in the case of exposures categorizing in Risk Class 1 and 2. However, several aspects besides the Risk Class can be relevant in a broad risk management context.

Table 4. Approach for risk classification.

Exposure	SAMOE	Risk Class	Concern level[a]
> $SARP_{high}$	< 0.01	Class 5	high
$SARP_{mod}$ to $SARP_{high}$	0.01 - 0.1	Class 4	moderate-to-high
$SARP_{low}$ to $SARP_{mod}$	0.1 - 1	Class 3	low-to-moderate
$SARP_{low}/10$ to $SARP_{low}$	1 - 10	Class 2	no-to-low
< $SARP_{low}/10$	> 10	Class 1	no

[a] While the concern level is regarded to increase gradually as the SAMOE decreases, details regarding this relationship depend on the chemical and the health effects it may cause. The comparison and ranking of chemicals according to health concerns applies at the level of the Risk Class, and currently represents a rough classification.

Table 5. Approach for assessment of the uncertainty in the risk classification.

SAMOE ×$SAMOE_U$[a]	Uncertainty Class	Uncertainty level
25^{th} and/or 75^{th} percentile outside selected Risk Class	Class 3	high
10^{th} and/or 90^{th} percentile outside selected Risk Class	Class 2	moderate
10^{th} and/or 90^{th} percentile within selected Risk Class	Class 1	low

[a] The output from the uncertainty model (section 4, equation 9) is a distribution describing factor deviations from the point estimate of the SAMOE. The multiplication SAMOE × $SAMOE_U$ will translate the results (the distribution) at the level of the absolute SAMOE scale.

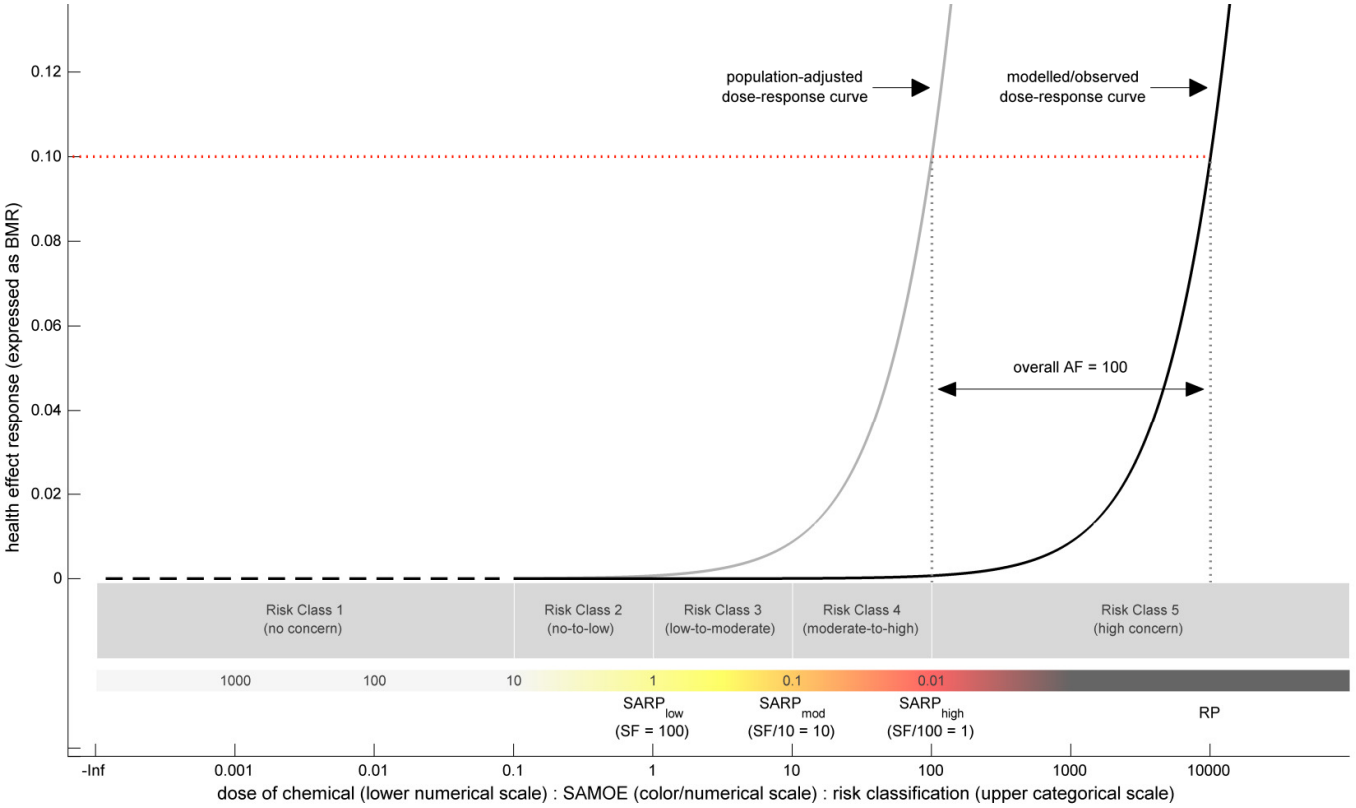


Figure 3a: Illustration of the approaches behind the Risk Thermometer (SF = 100). The curve to the right represents the dose-response relationship for a "severe" critical health effect (SF = 100, Table 3). The reference point (RP) equals a BMD corresponding to a BMR level of 10 %. An exposure of 5 units would give a SAMOE of 0.2, which classifies in Risk Class 3 (low-to-moderate concern) [SAMOE = 10,000 / (100 x 100 x 5) = 0.2].

<u>The SAMOE approach (section 3, Table 3):</u>
1) A population-adjusted reference point (PARP) is derived by the application of adjustment factors (AFs) to the RP (equation 1-3, Table 2). In this example, the RP is based on experimental data, and the target population is the sensitive human (default overall AF = 100).
2) A severity-adjusted reference point (SARP) is derived by dividing the PARP with a severity factor (SF) of 100; the critical effect is "severe" in this example (equation 4-5, Table 3).
3) The severity-adjusted margin of exposure (SAMOE) is calculated as the ratio between the SARP and the exposure to a chemical in a target population (equation 6).

<u>The risk classification approach (section 5, Table 4)</u>
SF application is regarded to result in a SARP associated with a low health concern, schematically similar to that associated with a reference point for a mild toxicity outcome (Table 3). Since SFs for "mild", "moderate", and "severe" effects are separated by factors of 10 (Table 3), application of SF, SF/10, and SF/100 is regarded to result in SARPs associated with "low", "moderate", and "high" concerns, respectively.
1) $SARP_{low}$ is 100x lower than the dose associated with a 10 % response in a "severe" effect. The margin to the RP is 10,000, which is regarded to be of low concern for compounds that are both genotoxic and carcinogenic (EFSA 2005), and also consistent with the EPA target range for cancer risk management (EPA 2005).
2) $SARP_{mod}$ is 10x lower than the dose associated with a 10 % response in a "severe" effect.
3) $SARP_{high}$ is the dose associated with a 10 % response in a "severe" effect.
These SARPs define the borders between four of the Risk Classes, and the border between Risk Class 1 and 2 is defined pragmatically. This categorization is based on risk management since the values used for the SF are currently not scientifically-based, but represent defaults similar to other default values used in risk assessment (Table 3).

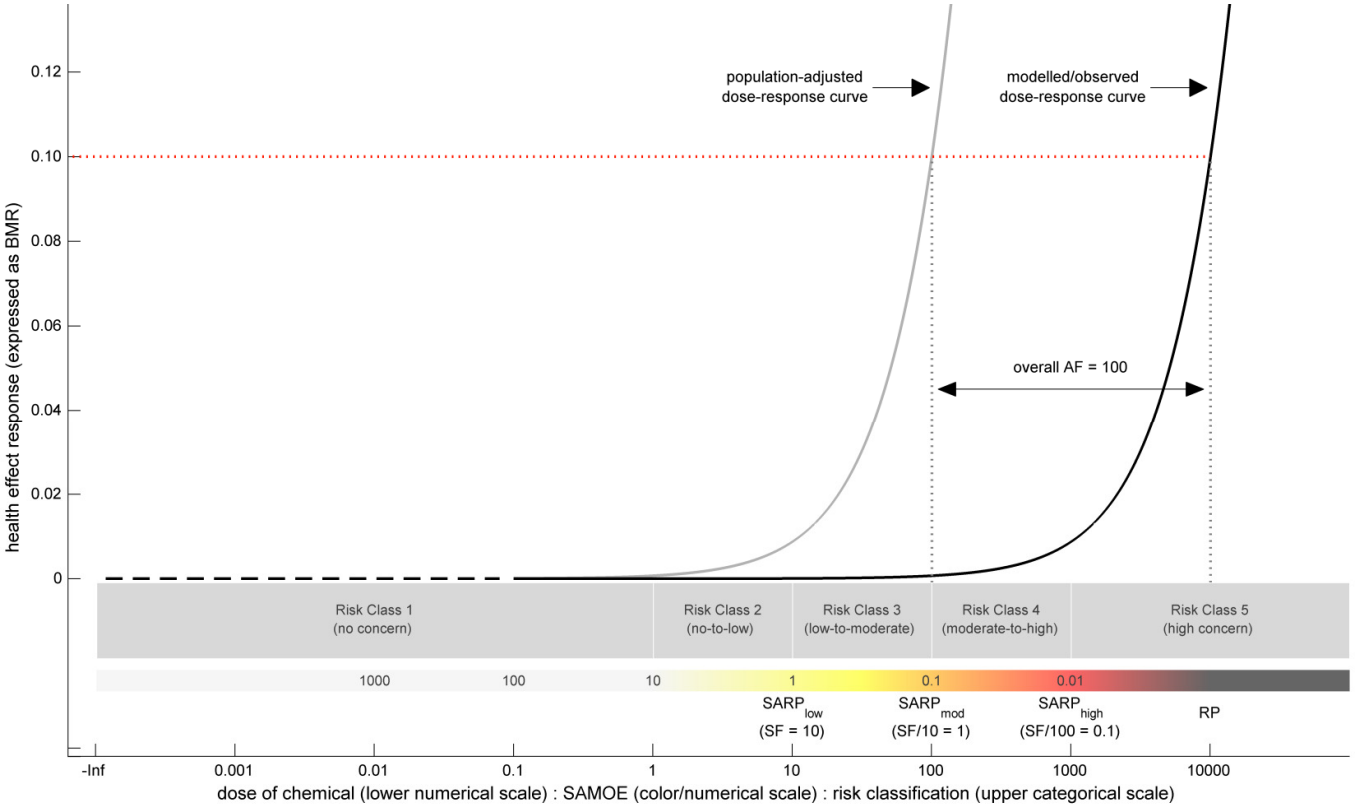


Figure 3b: Illustration of the approaches behind the Risk Thermometer (SF = 10). The curve to the right represents the dose-response relationship for a "moderate" critical health effect (SF = 10, Table 3). The reference point (RP) equals a BMD corresponding to a BMR level of 10 %. An exposure of 50 units would give a SAMOE of 0.2, which classifies in Risk Class 3 (low-to-moderate concern) [SAMOE = 10,000 / (100 x 10 x 50) = 0.2].

<u>The SAMOE approach (section 3, Table 3):</u>
1) A population-adjusted reference point (PARP) is derived by the application of adjustment factors (AFs) to the RP (equation 1-3, Table 2). In this example, the RP is based on experimental data, and the target population is the sensitive human (default overall AF = 100).
2) A severity-adjusted reference point (SARP) is derived by dividing the PARP with a severity factor (SF) of 10; the critical effect is "moderate" in this example (equation 4-5, Table 3).
3) The severity-adjusted margin of exposure (SAMOE) is calculated as the ratio between the SARP and the exposure to a chemical in a target population (equation 6).

<u>The risk classification approach (section 5, Table 4)</u>
SF application is regarded to result in a SARP associated with a low health concern, schematically similar to that associated with a reference point for a mild toxicity outcome (Table 3). Since SFs for "mild", "moderate", and "severe" effects are separated by factors of 10 (Table 3), application of SF, SF/10, and SF/100 is regarded to result in SARPs associated with "low", "moderate", and "high" concerns, respectively.
1) $SARP_{low}$ is 10x lower than the dose associated with a 10 % response in a "moderate" effect.
2) $SARP_{mod}$ is the dose associated with a 10 % response in a "moderate" effect.
3) $SARP_{high}$ is 10x higher than the dose associated with a 10 % response in a "moderate" effect.
These SARPs define the borders between four of the Risk Classes, and the border between Risk Class 1 and 2 is defined pragmatically. This categorization is based on risk management since the values used for the SF are currently not scientifically-based, but represent defaults similar to other default values used in risk assessment (Table 3).

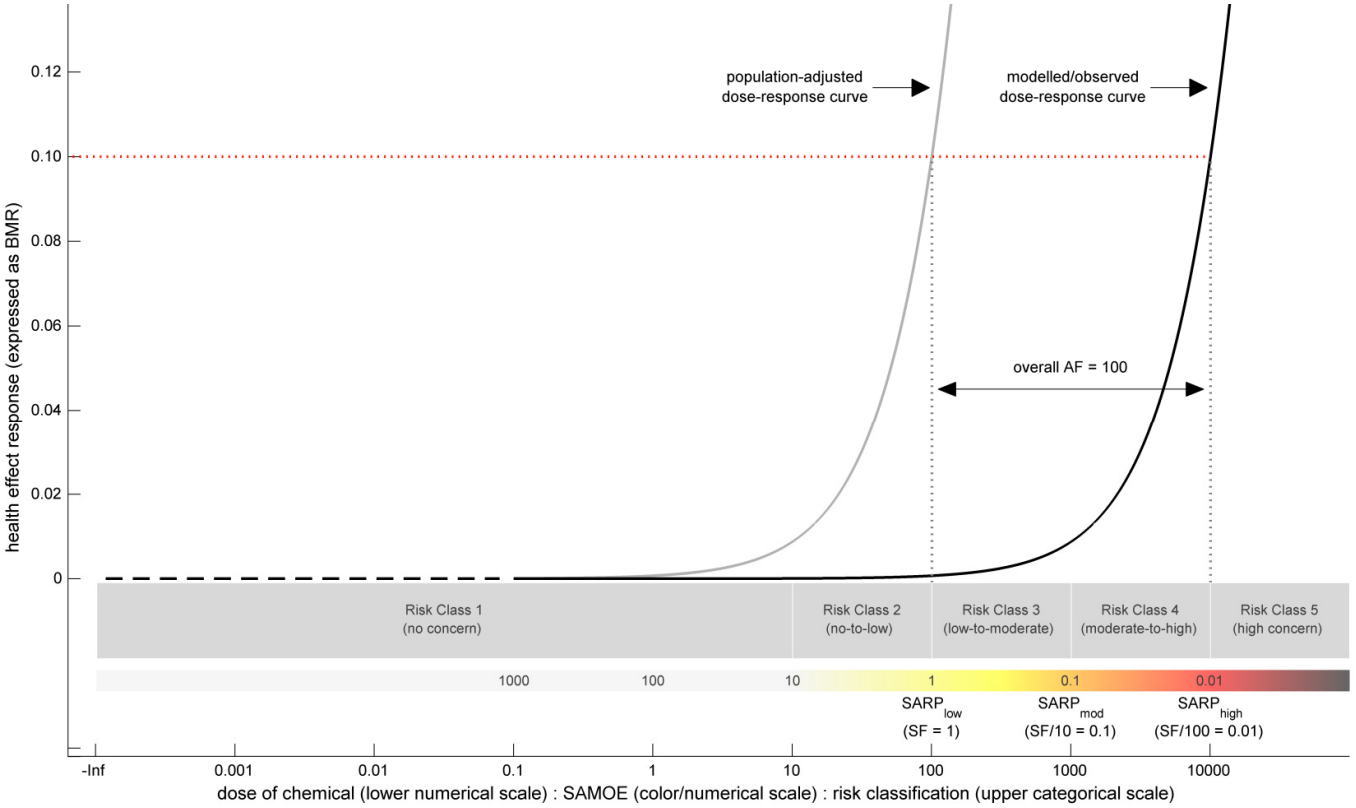


Figure 3c: Illustration of the approaches behind the Risk Thermometer (SF = 1). The curve to the right represents the dose-response relationship for "mild" critical health effect (SF = 1, Table 3). The reference point (RP) equals a BMD corresponding to a BMR level of 10 %. An exposure of 500 units would give a SAMOE of 0.2, which classifies in Risk Class 3 (low-to-moderate concern) [SAMOE = 10,000 / (100 x 1 x 500) = 0.2].

<u>The SAMOE approach (section 3, Table 3):</u>
1) A population-adjusted reference point (PARP) is derived by the application of adjustment factors (AFs) to the RP (equation 1-3, Table 2). In this example, the RP is based on experimental data, and the target population is the sensitive human (default overall AF = 100).
2) A severity-adjusted reference point (SARP) is derived by dividing the PARP with a severity factor (SF) of 1; the critical effect is "mild" in this example (equation 4-5, Table 3).
3) The severity-adjusted margin of exposure (SAMOE) is calculated as the ratio between the SARP and the exposure to a chemical in a target population (equation 6).

<u>The risk classification approach (section 5, Table 4)</u>
SF application is regarded to result in a SARP associated with a low health concern, schematically similar to that associated with a reference point for a mild toxicity outcome (Table 3). Since SFs for "mild", "moderate", and "severe" effects are separated by factors of 10 (Table 3), application of SF, SF/10, and SF/100 is regarded to result in SARPs associated with "low", "moderate", and "high" concerns, respectively.
1) $SARP_{low}$ is the dose associated with a 10 % response in a "mild" effect.
2) $SARP_{mod}$ is 10x higher than the dose associated with a 10 % response in a "mild" effect.
3) $SARP_{high}$ is 100x higher than the dose associated with a 10 % response in a "mild" effect.
These SARPs define the borders between four of the Risk Classes, and the border between Risk Class 1 and 2 is defined pragmatically. This categorization is based on risk management since the values used for the SF are currently not scientifically-based, but represent defaults similar to other default values used in risk assessment (Table 3).

Text box 3. Comparison of the Risk Thermometer vs. the traditional approach for risk characterization

In practice, the severity-adjusted margin of exposure (SAMOE) approach may be more or less protective/conservative, in relation to the traditional approach, for individual chemicals depending on the overall adjustment factor (overall AF) and the definition of the RP used in the process of HBGV development. At the level of the risk classification approach (section 5) the Risk Thermometer is generally regarded not to be fundamentally more protective/conservative than the traditional approach. These conclusions are based on the considerations described below.

The Risk Thermometer is a tool for comparative risk characterization, and the final result is a categorization of chemical exposures/risks into one of five "Risk Classes". Currently, quantitative risk characterization of chemicals is performed without reference to how the assessment for a given chemical stands relative to the assessment of another chemical. Thus, the Risk Thermometer (and the underlying SAMOE measure) is not directly comparable to the traditional approach. If the traditional approach was also designed for comparative risk characterization, and e.g., systematically provided lower rankings compared to the Risk Thermometer, the latter could be considered to be more protective/conservative. However, such comparison cannot strictly be made.

Comparison at the level of the severity-adjusted margin of exposure (SAMOE) approach

Application of a severity factor (SF) of 100 in the SAMOE approach provides an overall safety margin similar to that generally regarded to be adequate for compounds that are both genotoxic and carcinogenic (e.g., see Figure 3a). As discussed in section 2.1, an assessment factor (AF) for the severity of effects is, however, not systematically used for non-genotoxic compounds, but rather recommended on a case by case basis (ECHA 2012; EFSA 2012; WHO/IPCS 2009; WHO 2011). Thus, the (primary) severity-adjusted reference point ($SARP_{low}$, see Figure 3) becomes more protective than a *default* health-based guidance value (HBGV) for specific non-genotoxic chemicals with a SF set to a value larger than 1. Observe that "default HBGV" herein refers to RP/AFs (equation 1-2), where AF application relates to population-adjustments only, and does not describe risk/effect reduction in the RP (the standard response change in the RP is 10 % in the SAMOE approach).

Two *default* HBGVs may not provide the same level of protection if they are based on health effects that differ in severity, even if they may both be "protective" without application of SFs. Introduction of the element of severity is regarded to make the SARP/s (see Figure 3) formally more comparable across health effects than a HBGV, or similar. This is the reason for the SF application, but may indirectly make $SARP_{low}$ (see Figure 3) more protective than a default HBGV (for some non-genotoxic chemicals). In practice, however, other aspects may also determine if $SARP_{low}$ is more protective than a HBGV:

- If a "severe" effect is used for establishment of a HBGV it is likely that extra safety measures (e.g., an extra AF) are applied, similar to the SF application in the SAMOE approach. For example, in the case of lead induced toxicity EFSA (2010) concluded that a margin of exposure of 10 or greater would be sufficient to ensure that there was no appreciable risk of a clinically significant change in the prevalence of chronic kidney disease.

- Also, as far as possible the SAMOE approach uses a BMD_{10} as the RP (see section 3 and Text box 1). In situations when the RP used for traditional HBGV development is based on a "severe" effect the response associated with RP may sometimes be set lower than 10 % ; i.e., the 1 % level may be used if the data allows for this statistically, which increases the "level of protection" and indirectly adds an extra safety margin.

Text box 3. Comparison of the Risk Thermometer vs. the traditional approach for risk characterization

In conclusion, depending on the overall AF and the definition of the RP used in the process of HBGV development the primary reference point in the SAMOE approach ($SARP_{low}$, see Figure 3) may be more or less protective than a HBGV. However, a key point is that use of the SF is consistent and systematic for all hazards. This is necessary in order to compare and prioritize hazards. A traditional approach based on case by case assumptions would not be justified for this purpose.

Comparison at the level of the risk classification approach

In the risk classification approach not only $SARP_{low}$ but also $SARP_{mod}$ and $SARP_{high}$ are used as reference levels that define borders between the Risk Classes (see Figure 3). At the level of risk classification, the Risk Thermometer is regarded not to be fundamentally more protective (if at all more protective) than the traditional approach. It is regarded that exposures (at population level) that are in the range of a HBGV, or similar, would most likely classify in Risk Class 3 (low-to moderate concern) which represents the midpoint of the risk classification scale. Below are descriptions of exposure situations that correspond to Risk Class 3:

1) Exposures somewhat above (a factor 1-10 higher than) the population-adjusted reference point (HBGV = PARP = RP/AFs) for Category 1a effects (Table 3).
2) Exposures in the range of (within a factor 3.16 higher/lower than) the PARP for Category 1b or 2a effects (Table 3).
3) Exposures somewhat below (a factor 1-10 lower than) the PARP for Category 1c, 2b, or 3a effects (Table 3).
4) Exposures 3.16 to 31.6 times lower than the PARP for Category 2c or 3b effects (Table 3). In this case it can be discussed if exposures at the PARP would in fact be sufficiently protective; e.g., see the example of lead toxicity discussed above that would classify in Category 2c (chronic kidney disease).
5) Exposures 10 to 100 times lower than the PARP for Category 3c effects (Table 3). Exposures at the PARP appear in this case not to be sufficiently protective, e.g., they would correspond to a 10 % increased risk for cancer, malformations, decreased fertility at population level, and would classify in Risk Class 4/5. The use of extra safety margins would probably be warranted in case of traditional HBGV development.

Exposures in Risk Class 3 may depending on the particular situation require further considerations and application of risk management measures, including dietary advice or regulatory initiatives, and collection of more information to fill data gaps. From a risk perspective, the application of such measures is more likely to be relevant in the case of exposures categorizing in Risk Class 4 and 5, while it seems not likely to be needed in the case of exposures categorizing in Risk Class 1 and 2. However, it should be noted that several aspects besides the Risk Class may be relevant in a broad risk management perspective.

6 Risk Thermometer examples

In this section examples of practical application of the Risk Thermometer are given. These graphical illustrations (Figure 4) and associated numerical results (Table 6A-6E) are intended for evaluation of the underlying approaches discussed in sections 3-5, only. The examples do not reflect formal use of the Risk Thermometer by the NFA.

All examples are based on exposure data from market basket analysis, which implies that the target population in these examples may be considered to be the adult average consumer in Sweden. Moreover, the sensitive individual is not the target group. Rather, the analyses concern the average individual both in terms of exposure and susceptibility, and represent reference scenarios. Results will differ for other target populations.

Importantly, results from the Risk Thermometer apply to the target population under investigation. Thus, aspects of total public health burden, e.g., taking population size into account, are not explicitly included. The consideration of such aspects needs to be made separately as part of further risk management. The examples cover dietary exposure to lead, dioxin, cadmium, hexachlorobenzene (HCB), and bisphenol A (BPA) (Figure 4 and Table 6A-6E).

Comments regarding the point estimates of the SAMOE in the examples

For convenience the overall equation for the SAMOE (equation 7) is given below

$$SAMOE = \frac{RP}{AF} \times \frac{1}{AF_{BMR}} \times \frac{1}{SF} \times \frac{1}{E}$$

The examples of lead, dioxin, and cadmium describes the situation when human data has been used for RP derivation, and thus no AFs for population adjustment are applied in the case of these chemicals (observe that the target population is not the sensitive individual in the examples). For both lead and dioxin the RP is based on quite severe effects, and SFs of $10^{1.5}$ are applied in both cases (Table 6A and 6B). The impact of applied default values on the SAMOE is higher for dioxin than for lead (Table 6A and 6B: see the MOE/SAMOE ratios). This is due the application of an extra AF = 3 in the case of dioxin since the RP is a LOAEL. Both lead and dioxin categorize in Risk Class 3, and in both cases the uncertainty associated with the risk classification is “moderate” and “low” in the downward and upward direction, respectively (Table 6A and 6B, Figure 4).

For cadmium, the SAMOE is about a factor 10 higher than the SAMOEs for lead and dioxin. This is mainly because the applied SF is a factor 10 lower than for

lead and dioxin (Table 6A-C; chronic kidney disease/reproductive effects for lead/dioxin vs. change in kidney marker for cadmium). Cadmium categorizes in Risk Class 2, and the uncertainty associated with the risk classification is “low” in both the downward and upward direction (Table 6C, Figure 4).

HCB and BPA categorize in Risk Class 1. Among all examples, the impact of applied default values on the SAMOE is the highest for HCB (Table 6D: MOE/SAMOE ratio = 1000). This is due to a large SF = 10^2 in combination with an AF = 10 since the RP is based on animal data. Even so, the SAMOE for HCB is low which is indicative of a low exposure; this may also be concluded from the large MOE, i.e., MOE = 840,000 (Table 6D).

The SAMOE is even lower for BPA. The SF applied for BPA is the same as that for cadmium (Table 6C and 6E: change in kidney marker for cadmium and change in mean relative kidney weight for BPA). Also, in similarly to cadmium the over-all impact of applied default values on the SAMOE for BPA is quite low (Table 6C and 6E: MOE/SAMOE = 3.2 for cadmium and 7.9 for BPA). Thus, the BPA exposure is much lower relative to the cadmium exposure. The comparatively low exposure to BPA is a result of the use of new Swedish market basket data; the type of exposure data that is used in all examples. Observe that the five examples are based on the principal/primary critical effect identified in the risk assessments used as basis for RP derivation (Table 6A-6E). Potential critical effects besides “mean relative kidney weight” have been discussed in the case of BPA. Formal application of the Risk Thermometer may for example require additional consid-eration in this respect.

Comments regarding the overall uncertainty in the SAMOE in the examples

The overall uncertainty, measured by the ratio between the upper 95th and lower 5th confidence limits of the uncertainty distribution, is the lowest for cadmium (Table 6C: U95/L05 = 3.5). This is partly related to a low data driven uncertainty in the exposure (a small difference between results based on lower and upper bound settings for concentration values below the LOD/LOQ), and the application of one default value, only (the SF).

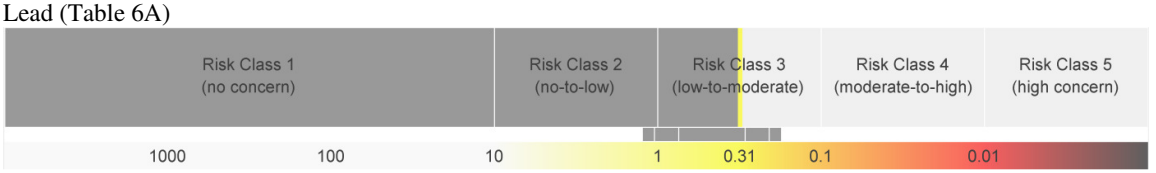
The uncertainty is slightly higher for dioxin (Table 6B: U95/L05 = 4.8); the data driven uncertainty in the exposure is low, but two default values are applied (the SF and also AF_{BMR} for LOAEL adjustment).

The uncertainty for HCB is somewhat higher than that for dioxin (Table 6D: U95/L05 = 5.9); the data driven uncertainty in the exposure is low, but a total of three default values are applied in the case of HCB (two AFs, and the SF). As noted in section 4, quantitative standards for the uncertainty are assigned for each default value that is applied, and it is generally regarded that the uncertainty in the SAMOE increases with an increasing number of applied default values.

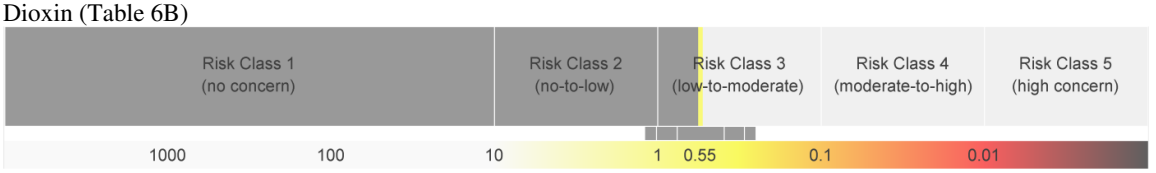
For lead the uncertainty is the second highest (Table 6A: U95/L05 = 7.1). This is related to a comparatively high data driven uncertainty in the exposure, since the uncertainty in the RP is quite low, and since only one default value is applied (the SF).

For BPA the uncertainty is the highest (Table 6E: U95/L05 = 15). This is mainly due to a large data driven uncertainty in the RP, but also due to data driven uncertainties in the exposure, and the fact that two default values are applied (one AF and the SF).

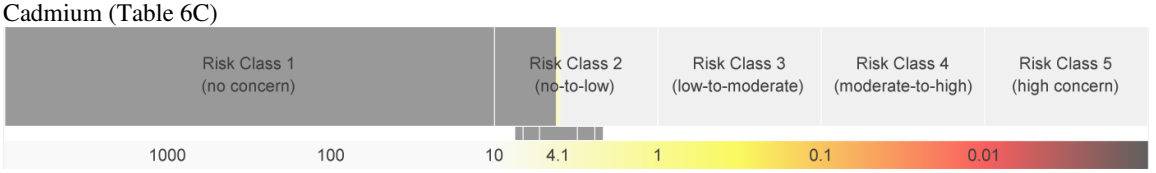
Lead (Table 6A)



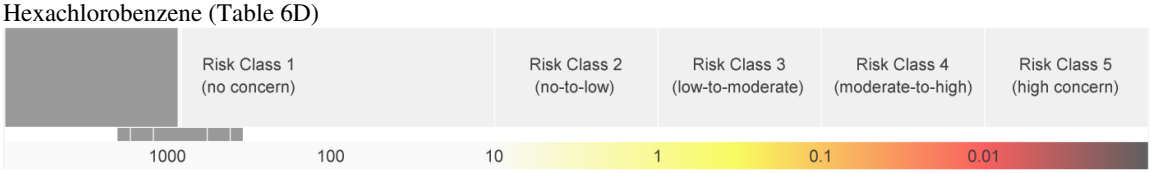
Dioxin (Table 6B)



Cadmium (Table 6C)



Hexachlorobenzene (Table 6D)



Bisphenol A (Table 6E)

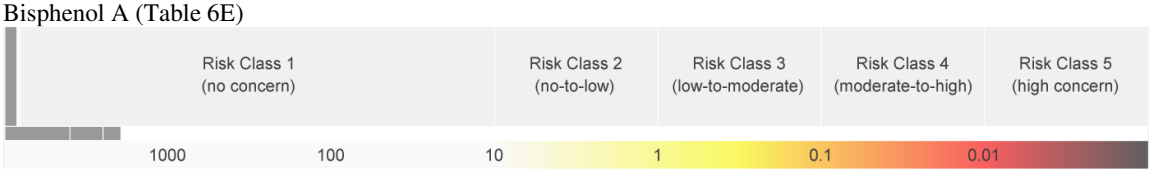


Figure 4: Illustrations of the results in Tables 6A-6E.
The wide gray bars describe the SAMOE estimate that classifies in a particular Risk Class that corresponds to a level of health concern (see Table 4). The thin gray bars describe the uncertainty in the SAMOE. The full uncertainty interval describes the lower 5th and upper 95th confidence limits. The 10th/90th confidence limits, as well as the 25th/75th confidence limits are also shown. For lead and dioxin, the 90 % confidence limit spans another Risk Class (Risk Class 2). Therefore the uncertainty in the risk classification is “moderate” (in the downward direction) for these two compounds (see also Table 5 and Table 6A-E).

Figur 4: Swedish translation.
Illustrationer av resultaten i Tabell 6A-6E. Dessa exempel är enbart tänkta för utvärdering av metoderna som Risktermometerverktyget baseras på. De breda grå staplarna visar storleken på SAMOE-värdet som klassificerar i en av de fem riskklasserna som beskriver olika grader av hälsoangelägenhet (se Tabell 4). De tunna grå staplarna visar osäkerhets-intervallet för SAMOE-värdet. Ändarna av intervallet beskriver den 5:e och 95:e konfi-densgränsen. Linjer som visare den 10:e respektive 90:e konfidensgränsen samt den 25:e respektive 75:e konfidensgränsen illustreras också. För bly och dioxin glider den 90:e konfidensgränsen över till en annan riskklass (Risk Class 2). En viss osäkerhet i riskklas-sificeringen (i nedåtgående riktning) bedöms därför finnas med avseende på dessa två substanser (se även Tabell 5 och Tabell 6A-6E).

Table 6A. Illustrative results using lead exposure in the general population as an example. Results are intended for model evaluation, only.

Results		**Comment/description**
RISK CLASS	3	Low-to-moderate concern
Uncertainty Class (upward)	1	Low uncertainty in risk classification upwards
Uncertainty Class (downward)	2	Moderate uncertainty in risk classification downwards
SAMOE	0.31	Severity-adjusted margin of exposure
SAMOE uncertainty - U95/L05	7.1	Overall uncertainty in the SAMOE
MOE	9.9	MOE = RP / exposure
MOE / SAMOE	32	Describes the total impact of AFs and the SF
Input: SAMOE approach		
Compound	lead	
Target population	general population	The adult average consumer
Exposure: estimate	0.0676 µg/kg/day	Preliminary analysis of data from Livsmedelsverket (2012a and b)
RP: type	BMD	
RP: estimate	0.67 µg/kg/day	EFSA (2010). BMD (in units µg/kg/day) derived by toxikokinetic model; BMD = 16 / (0.4 * 60) = 0.67.
BMR: level	0.1	Standard BMR
BMR: definition	extra risk	
AF RP-adjustment	1	No response adjustment needed (standard BMR)
AF interspecies-TK	1	Data on target population, no AF needed
AF interspecies-TD	1	Data on target population, no AF needed
AF intraspecies-TK	1	Non-sensitive target population (average consumer)
AF intraspecies-TD	1	Non-sensitive target population (average consumer)
Classification	hepato/nephro. 2c	See Table 3
Severity, x (SF = 10^x)	1.5	
Endpoint	chronic kidney disease	Study population of 14,778 adults at least 20 years old who participated in the NHANES (1999-2006) study
Input: Uncertainty Model		
Exposure: UB[a]	0.117 µg/kg/day	Concentration values below LOD/LOQ = LOD/LOQ
Exposure: LB[a]	0.0179 µg/kg/day	Concentration values below LOD/LOQ = 0
Reference point: UB	0.71 µg/kg/day	BMDU (extrapolated: BMDU = BMD × BMD/BMDL)
Reference point: LB	0.63 µg/kg/day	EFSA (2010). BMDL (in units µg/kg/day) derived by toxikokinetic model; BMDL = 15 / (0.4 * 60) = 0.63
Default values (AFs, SF): UB	Quantitative standard	Applied to one default value. see Text box 2
Default values (AFs, SF): LB	Quantitative standard	Applied to one default value. see Text box 2

[a] UB: upper bound; LB: lower bound.

Table 6B. Illustrative results using polychlorinated dioxin and biphenyl (PCDD-PCB) exposure in the general population as an example. Results are intended for model evaluation, only.

Results		**Comment/description**
RISK CLASS	3	Low-to-moderate concern
Uncertainty Class (upward)	1	Low uncertainty in risk classification upwards
Uncertainty Class (downward)	2	Moderate uncertainty in risk classification downwards
SAMOE	0.55	Severity-adjusted margin of exposure
SAMOE uncertainty - U95/L05	4.8	Overall uncertainty in the SAMOE
MOE	52	MOE = RP / exposure
MOE / SAMOE	95	Describes the total impact of AFs and the SF
Input: SAMOE approach		
Compound	PCDD-PCB	
Target population	general population	The adult average consumer
Exposure: estimate	0.384 pg/kg/day	Preliminary analysis of data from Livsmedelsverket (2012a and b)
RP: type	LOAEL	
RP: estimate	20 pg/kg/day	EPA (2012)
BMR: level	-	
BMR: definition	-	
AF RP-adjustment	3	Standard adjustment for LOAEL. See Text Box 1
AF interspecies-TK	1	Data on target population, no AF needed
AF interspecies-TD	1	Data on target population, no AF needed
AF intraspecies-TK	1	Non-sensitive target population (average consumer)
AF intraspecies-TD	1	Non-sensitive target population (average consumer)
Classification	reproduct. 3b	See Table 3
Severity, x ($SF = 10^x$)	1.5	
Endpoint	decreased sperm count/motility	Epidemiologic cohort study, men exposed as boys
Input: Uncertainty Model		
Exposure: UB[a]	0.44 pg/kg/day	Concentration values below LOD/LOQ = LOD/LOQ
Exposure: LB[a]	0.33 pg/kg/day	Concentration values below LOD/LOQ = 0
Reference point: UB	Quantitative standard	See Text box 2
Reference point: LB	Quantitative standard	See Text box 2
Default values (AFs, SF): UB	Quantitative standard	Applied for two default values. See Text box 2
Default values (AFs, SF): LB	Quantitative standard	Applied for two default values. See Text box 2

[a] UB: upper bound; LB: lower bound.

Table 6C. Illustrative results using cadmium exposure in the general population as an example. Results are intended for model evaluation, only.

Results		**Comment/description**
RISK CLASS	2	No-to-low concern
Uncertainty Class (upward)	1	Low uncertainty in risk classification upwards
Uncertainty Class (downward)	1	Low uncertainty in risk classification downwards
SAMOE	4.1	Severity-adjusted margin of exposure
SAMOE uncertainty - U95/L05	3.5	Overall uncertainty in the SAMOE
MOE	13	MOE = RP / exposure
MOE / SAMOE	3.2	Describes the total impact of AFs and the SF
Input: SAMOE approach		
Compound	cadmium	
Target population	general population	The adult average consumer
Exposure: estimate	0.112 µg/kg/day	Preliminary analysis of data from Livsmedelsverket (2012a and b)
RP: type	BMD	
RP: estimate	1.44 µg/kg/day	An extra AF of 4 was used in EFSA (2009b) to account for sensitive individuals, which is not the target group in these illustrations. The BMDL was herein recalculated as 0.36 × 4 = 1.44. This BMDL was used as a surrogate for the BMD (the BMD and BMDL expressed in terms of µg/g creatinine were very close).
BMR: level	0.05	
BMR: definition	extra risk	
AF RP-adjustment	1	No adjustment since BMDs and BMDLs (expressed in terms of µg/g creatinine) associated with BMRs of 5 and 10 % were similar
AF interspecies-TK	1	Data on target population, no AF needed
AF interspecies-TD	1	Data on target population, no AF needed
AF intraspecies-TK	1	Non-sensitive target population (average consumer)
AF intraspecies-TD	1	Non-sensitive target population (average consumer)
Classification	hepato/nephro. 2a	See Table 3
Severity, x (SF = 10^x)	0.5	
Endpoint	change in beta-2-microglobulin	
Input: Uncertainty Model		
Exposure: UB[a]	0.113 µg/kg/day	Concentration values below LOD/LOQ = LOD/LOQ
Exposure: LB[a]	0.112 µg/kg/day	Concentration values below LOD/LOQ = 0
Reference point: UB	Quantitative standard	See Text box 2
Reference point: LB	Quantitative standard	See Text box 2
Default values (AFs, SF): UB	Quantitative standard	Applied for one default value. See Text box 2
Default values (AFs, SF): LB	Quantitative standard	Applied for one default value. See Text box 2

[a] UB: upper bound; LB: lower bound.

Table 6D. Illustrative results using hexachlorobenzene (HCB) exposure in the general population as an example. Results are intended for model evaluation, only.

Results		**Comment/description**
RISK CLASS	1	No concern
Uncertainty Class (upward)	1	Low uncertainty in risk classification upwards
Uncertainty Class (downward)	-	Not applicable for lowest Risk Class
SAMOE	840	Severity-adjusted margin of exposure
SAMOE uncertainty - U95/L05	5.9	Overall uncertainty in the SAMOE
MOE	840,000	MOE = RP / exposure
MOE / SAMOE	1000	Describes the total impact of AFs and the SF
Input: SAMOE approach		
Compound	HCB	
Target population	general population	The adult average consumer
Exposure: estimate	0.961 ng/kg/day	Preliminary analysis of data from Livsmedelsverket (2012a and b)
RP: type	BMD	
RP: estimate	810,000 ng/kg/day	WHO/IPCS (1997)
BMR: level	0.05	
BMR: definition	extra risk	
AF RP-adjustment	1	No response-adjustment performed due to lack of dose-response information
AF interspecies-TK	3.98	Default AF
AF interspecies-TD	2.51	Default AF
AF intraspecies-TK	1	Non-sensitive target population (average consumer)
AF intraspecies-TD	1	Non-sensitive target population (average consumer)
Classification	cancer 3c	See Table 3
Severity, x (SF = 10^x)	2	
Endpoint	cancer	Neoplastic liver effects in rats
Input: Uncertainty Model		
Exposure: UB[a]	0.961 ng/kg/day	Concentration values below LOD/LOQ = LOD/LOQ
Exposure: LB[a]	0.961 ng/kg/day	Concentration values below LOD/LOQ = 0
Reference point: UB	Quantitative standard	See Text box 2
Reference point: LB	Quantitative standard	See Text box 2
Default values (AFs, SF): UB	Quantitative standard	Applied for three default values. See Text box 2
Default values (AFs, SF): LB	Quantitative standard	Applied for three default values. See Text box 2

[a] UB: upper bound; LB: lower bound.

Table 6E. Illustrative results using bisphenol A (BPA) exposure in the general population as an example. Results are intended for model evaluation, only.

Results		**Comment/description**
RISK CLASS	1	No concern
Uncertainty Class (upward)	1	Low uncertainty in risk classification upwards
Uncertainty Class (downward)	-	Not applicable for lowest Risk Class
SAMOE	8200	Severity-adjusted margin of exposure
SAMOE uncertainty - U95/L05	15	Overall uncertainty in the SAMOE
MOE	65,000	MOE = RP / exposure
MOE / SAMOE	7.9	Describes the total impact of AFs and the SF
Input: SAMOE approach		
Compound	BPA	
Target population	general population	The adult average consumer
Exposure: estimate	0.0367 µg/kg/day	Livsmedelsverket (2014)
RP: type	BMD	
RP: estimate	2380 µg/kg/day	EFSA (2015). Application of human equivalent dose factor (HEDF) of 0.068 to animal BMD; BMD = 35,000 × 0.068 = 2380
BMR: level	0.1	Standard BMR
BMR: definition	relative effect	
AF RP-adjustment	1	No response adjustment needed (standard BMR)
AF interspecies-TK	1	No AF needed; already accounted for in the RP derivation by application of HEDF
AF interspecies-TD	2.51	Default AF
AF intraspecies-TK	1	Non-sensitive target population (average consumer)
AF intraspecies-TD	1	Non-sensitive target population (average consumer)
Classification	hepato/nephro. 2a	See Table 3
Severity, x ($SF = 10^x$)	0.5	
Endpoint	Increased mean relative kidney weight	Two-generation study in mice
Input: Uncertainty Model		
Exposure: UB[a]	0.0466 µg/kg/day	Concentration values below LOD/LOQ = LOD/LOQ
Exposure: LB[a]	0.0269 µg/kg/day	Concentration values below LOD/LOQ = 0
Reference point: UB	7400 µg/kg/day	EFSA (2015). BMDU = 108,900 × 0.068 = 7400
Reference point: LB	609 µg/kg/day	EFSA (2015). BMDL = 8,960 × 0.068 = 609
Default values (AFs, SF): UB	Quantitative standard	Applied for two default values. See Text box 2
Default values (AFs, SF): LB	Quantitative standard	Applied for two default values. See Text box 2

[a] UB: upper bound; LB: lower bound.

7 Future developments

The Risk Thermometer and its underlying elements may be subject to further developments, which may include but is not limited to the following.

- The equations for the SAMOE may be generalized so that the input parameters (i.e., the RP, AFs, SF, and E) are represented by distributions, instead of point estimates, accounting for both variability and uncertainty. Such approaches have been discussed in the case of a traditional margin of exposure approach (e.g., van der Voet and Slob 2007; Kalantari et al. 2013), which could be extended to the SAMOE. Also, while a generalization to the case of cumulative exposure was introduced (equation 8) it might also be appropriate to extend this to other measures of combined exposure, e.g., the hazard index.

- The SAMOE approach is regarded to benefit from more standardized definitions of the RP. The present version mainly relies on RPs established at international level, which may be based on different data formats (quantal or continuous data) and different BMR definitions. Ongoing initiative, for example in the U. S., envisions that future toxicity tests will be conducted in human cells or cell lines in vitro by evaluating cellular responses in a suite of toxicity pathway assays using high-throughput tests. Risk assessments would be performed based on results of such tests, and the equivalents of today's health based guidance values would aim, according to the National Research Council, at representing dose levels that avoid significant perturbations of the toxicity pathways in exposed human populations (NCR, 2007). A future use of in vitro data for risk assessment may result in that more standardized RPs will be used. For example since the use of in vitro data significantly increases the amount of dose-response data that needs to be processed the use of standardized modelling protocols, including standardized RPs, has been suggested (Wignall et al. 2014; Thomas et al. 2013; Sand et al. 2014 manuscript in preparation). The standard BMD corresponding to a BMR of 10 % in the present approach may thus be revised in the future.

- The SAMOE approach compares chemicals based on the exposure situation in relation to the severity-adjusted reference point (SARP). Van der Voet et al. (2009) has suggested the use of health impact criterions (HICs) for defining sets of RPs used for margin of exposure calculations. This is a generalization of the concept of defining the RP as corresponding to a BMR level that is non-adverse such that a set of RPs are established that corresponds to BMR levels associated with "low", "moderate", or "severe" HICs. Such BMR levels will depend on the risk assessment endpoint. As discussed in Text box 1, there is generally no consensus on BMR levels corresponding to low health impacts, and the extension of this to also encompass "moderate" and "severe"

health impacts clearly represents a challenge. The SAMOE approach used herein categorizes “mild”, “moderate”, and “severe” toxicity outcomes at the level of the endpoint, rather than categorization of response levels. A consequence of the suggestion in van der Voet et al. (2009) is that the separation between e.g., moderate and severe HIC, in terms of exposure, will depend on the chemical and endpoint (i.e., the dose-response curve). In the current approach, however, the Risk Classes span constant exposure intervals. The classification scheme (Table 3) may be refined so that the equation for the SF ($SF = 10^{x}$) is better differentiated between and within the toxicity-specific subgroups. For example, a future scheme may focus more on the categorization of chain of events (or paths) across the scheme, which differ in terms of the range of the SF so that the separation between “mild”, “moderate” and “severe” is category specific. As noted in Table 3, future studies may even investigate if RPs for “mild”, “moderate”, and “severe” effects, or similar, for a specific chemical and “critical pathway” directly can be used as basis for establishing exposure reference levels in a multidimensional context. This would be compound specific and data driven equivalents to $SARP_{low}$, $SARP_{mod}$, and $SARP_{high}$ that are currently derived by application of SF, SF/10, and SF/100, and define borders between four of the Risk Classes (see Figure 3).

· Comparative approaches based on the disability-adjusted life years (DALYs) (Lopez and Murray 1998), or similar metrics describing disease burden, may potentially be envisioned in the future for assessment of chemical exposure/risk. For example, Crettaz et al. (2002) and Pennington et al. (2002) discussed a DALY approach for chemicals based on low-dose linear extrapolation from the BMD_{10}. While not discussed in detail in this report, that type of DALY approach is proportionally related to the SAMOE approach so that measures from both approaches may be interpreted on a common risk classification scale (e.g., the scale in Table 4). In the medium term, this link between the SAMOE and DALY may be used as a first step to a more general framework for comparative risk characterization encompassing both chemical and microbiological risk; i.e., a SAMOE approach may be more intuitive for chemicals while a DALY approach may be more intuitive for microbiological agents. However, current DALY approaches for chemicals appear applicable for health effect describing probabilities, only; i.e., endpoints that can be translated in terms of incident cases of some disease. A challenge is to make the DALY concept, or similar, applicable also for other health outcomes, since the critical health effects used for chemical assessments often does not directly translate to disease, i.e., changes in enzyme/marker levels, relative organ weights, IQ etc. In the long term, a possible way forward may be to develop a framework for how “fraction of cases” may be determined, for example considering the chain of event that may ultimately lead to disease.

8 Conclusion

The Risk Thermometer for comparison of chemical risks associated with food consumption has been developed in this project. The tool consists of four parts: 1) a severity-adjusted margin of exposure (SAMOE) approach, which is an extension of the current approach for chemical risk characterization, 2) a model that describes the uncertainty in the SAMOE, 3) a risk classification approach that categorizes the SAMOE value in terms of health concern levels, and 4) a graphical front end that provides an illustration of the results.

By choice the Risk Thermometer is based on both scientific considerations (risk assessment) and value-based considerations (risk management). The scientific considerations concern the SAMOE approach (parts 1 and 2) except some aspects of the severity classification of health effects, and the value-based considerations concern the risk classification approach (part 3) and some aspects of the severity classification of health effects.

The Risk Thermometer aims to bridge the three elements of risk analysis (risk assessment, risk management, and risk communication). The approach is, however, in line with the important principle of an operational separation between risk assessment and risk management, since the set of default value-based severity factors are transparently defined prior to the assessment. This is for example similar to the application of default adjustment factors for inter- and intra-species differences in susceptibility. Revision of the Risk Thermometer will be considered as experience of using this approach in the process of risk analysis increases.

Importantly, results from the Risk Thermometer represent one basis for risk management. For example, they apply to the target population under investigation. Thus, aspects of total public health burden, taking population size into consideration is not explicitly included; such factors needs to be accounted for separately as part of further risk management.

The SAMOE approach is based on the traditional margin of exposure (MOE) or MOE related concepts used for risk characterization. As a starting point, it was regarded appropriate that the underlying scientific measure for risk comparison is based on principles, including data requirements and use of default values, which are similar to those applied in traditional quantitative risk characterization. A practical framework for comparative risk characterization that efficiently can be integrated in today's risk assessment, risk management, and risk communication workflow needs to be based on current methodology and risk assessment practice to a high extent. However, while the MOE indirectly relates to the probability of occurrence (or change in the response) of a health effect the severity of the health effect is generally not accounted for by this metric. "Probability" (or similar) and "severity" are in fact both important elements of the risk concept. This considera-

tion is of particular relevance herein since the objective of the Risk Thermometer involves comparative risk characterization across chemicals and health effects in contrast to applications of the traditional MOE approach.

The SAMOE approach satisfies the requirements associated with the Risk Thermometer by penalizing the traditional MOE value or similar, depending on the severity of the critical health effect used as basis for risk assessment. This is achieved by the systematic application of a severity factor that is determined from a developed health effect classification scheme. This scheme represents the key element of the SAMOE approach, and differentiates the SAMOE approach from more traditional margin of exposure approaches.

To appreciate the current limitations involved in comparative as well as ordinary risk characterization a semi-quantitative model that describes the uncertainty in the SAMOE estimate was also developed. This method involves determining the level and direction of uncertainties associated with each of the parameters of the SAMOE. Whenever possible data driven inputs are used in this model, and if data is not available semi-quantitative standards are used instead. The overall uncertainty in the SAMOE is in addition to the point estimate accounted for in the risk classification approach. It is regarded as an improvement to describe the overall uncertainty involved in risk characterization quantitatively as well as graphically. This helps to be better realizing that it sometimes may be quite significant. The uncertainty model may be further developed by defining more appropriate uncertainty distributions for each of the parameters of the SAMOE.

Under a risk classification approach the SAMOE estimate is categorized in terms of health concern levels. There are currently five Risk Classes. The NFA may further develop the approach for risk classification regarding statements about the level of health concern that is associated with each Risk Class. In the interim, the Risk Thermometer is regarded not to be fundamentally more protective than the traditional risk assessment approach. It is considered that exposures (at population level) that are in the range of a traditional health-based guidance value, or similar, would most likely classify in Risk Class 3 (low-to moderate concern) which represents the midpoint of the risk classification scale. Exposures in Risk Class 3 may depending on the particular situation require further considerations and application of risk management measures, which may include dietary advice or regulatory initiatives, and collection of more information to fill data gaps. From a risk perspective, the application of such measures is more likely to be relevant in the case of exposures categorizing in Risk Class 4 and 5, while it seems not likely to be needed in the case of exposures categorizing in Risk Class 1 and 2. However, it should be noted that several aspects besides the Risk Class may be relevant in a broad risk management context.

The use of the Risk Thermometer is currently limited to classification of chemical risks associated with chronic exposure via food (i.e., not acute effects). The tool may for example be used to assess and compare such exposures to environmental

contaminants, pesticides, food additives, chemicals used in food contact materials, as well as minerals/nutrients. A future challenge may be to generalize the concept of the Risk Thermometer to also cover acute effects associated with chemical exposure, and/or risks associated with microbiological agents. Also, the graphical front end of the tool will be further developed.

The main limitation of the underlying SAMOE approach is related to the diverse nature of endpoints used as critical health effect parameters in current chemical risk assessments, which complicates the determination of the severity factor; i.e., the parameter that mainly discriminates the SAMOE from other margin of exposure related measures. The classification of health effect parameters based on different data formats (continuous or quantal data) and reference point definitions is not straight-forward. It is regarded that methods for comparative risk characterization ultimately will benefit from the consideration of risk assessment parameters that are less diverse in nature, for example enabling more standardized establishment of reference points compared to current practice.

While there are challenges associated with the Risk Thermometer concept, the relative importance of exposures (at population level) depending on the type of health effects they may cause are issues that need to be considered as one part of risk assessment and/or risk management. More generally, the Swedish National Food Agency (NFA) needs to assess, rank/prioritize, and communicate chemicals risks with or without out a Risk Thermometer. The NFA regards it as an improvement to have an agreed and formalized approach prior to the risk assessment that also accounts for severity. This reduces for example the risk for subjective inclusion/exclusion of severity considerations, and introduces a higher transparency regarding how the severity of effect is allowed to impact, quantitatively, in the process of risk analysis. Also, the area of chemical risk assessment is regarded to benefit from the introduction and practical use of approaches that forces the interpretation of exposures or risks in a greater context. Consumer interests regarding health risks associated with food consumption may benefit from such developments, as well as the health agencies that are forced to prioritize the use of their resources with respect to risk related issues.

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Rapporter som utgivits 2014

1. Exponeringsuppskattningar av kemiska ämnen och mikrobiologiska agens – översikt samt rekommendationer om arbetsgång och strategi av S Sand, H Eneroth, B-G Ericsson och M Lindblad.
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5. Kontroll av bekämpningsmedelsrester i livsmedel 2011 och 2012 av P Fohgelberg, A Jansson och H Omberg.
6. Vad är det som slängs vid utgånget hållbarhetsdatum? – en mikrobiologisk kartläggning av utvalda kylvaror av Å Rosengren.
7. Länsstyrelsernas rapportering av livsmedelskontrollen inom primärproduktionen 2012 av L Eskilson och S Sylvén.
8. Riksmaten – vuxna 2010-2011, Livsmedels- och näringsintag bland vuxna i Sverige av E Amcoff, A Edberg, H Enghart Barbieri, A K Lindroos, C Nälsén, M Pearson och E Warensjö Lemming.
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Rapporter som utgivits 2015

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