Report on Public Consultation

Draft report on the Risk Thermometer

Content

1 Introduction and general response

The Swedish National Food Agency (NFA) is very thankful for all comments provided on the draft report. These comments have helped to improve the Risk Thermometer. For example, considerations and rational behind the tool, including its relation to more traditional approaches for quantitative risk assessment, are discussed in more detail in the final version of the report. The risk assessment and risk management elements of the Risk Thermometer are also better clarified, and some technical modifications of the approach have been made.

Comments were received from:

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

The comments indicated for example that the suggested approach can be used for risk comparison and enable risk prioritization. Some concerns were also raised for example suggesting that the Risk Thermometer is (much) more conservative that the traditional risk assessment approach. All comments provided can be found in Appendix A.

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

- Scientific considerations (risk assessment): the severity-adjusted margin of exposure (SAMOE) approach, except some aspects of the severity classification (see revised Table 3).
- Value-based considerations (risk management): some aspects of the severity classification and the risk classification approach.

The Risk Thermometer provides *one* basis for risk management. The approach is 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. For example, this is similar to the application of default adjustment factors for inter- and intra-species differences in susceptibility. The Risk Thermometer aims to bridge the three elements of risk analysis (risk assessment, risk management, and risk communication).

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 inputs (including the use of default values e.g., adjustment factors), 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 at the National Food Agency (NFA) needs to be based on current methodology and risk assessment practice to a high extent. However, while the traditional MOE indirectly relates to the probability of occurrence (or change in the response) of some health effect the severity of the health effect is generally not accounted for by this measure. "Probability" (or similar) and "severity" are both important elements of the risk concept, which e.g., is supported by the Codex definition of risk characterization (FAO/WHO 2008). This consideration is of particular relevance herein since the objective of the Risk Thermometer relates to comparative risk characterization across chemicals and *health effects* in contrast to applications of the traditional MOE approach.

Also, the relative importance of exposures (at population level) depending on the type of health effects they may cause are issues that ultimately need to be considered as one part of risk assessment and/or management 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.

The comments provided are addressed in this document. Some comments have been received in Swedish. However, all responses are given in English. A summary of all changes made to the report is given in section 2. Some comments received from different parties involve similar issues, and they will be addressed separately in section 3 "Common response". The comments provided from each party are thereafter specifically addressed.

2 Summary of changes made to the report

Title	The title has been slightly revised. We anticipate that updated versions of the tool will be released in the future.
Summary	Has been updated due to revisions made to the report.
Sammanfattning	Has been slightly revised.
Objective	The objective and mandate has been clarified.
Section 2	Slightly revised. Elements in the Risk Thermometer that relates to scientific (risk assessment) and value-based (risk management) considerations have been better clarified (see also revised summary, Table 3, section 5, and conclusion). Also, it is clarified that to satisfy the objective the suggested approach needs to be based on current risk assessment practice to a high extent.
Section 2.1	A Codex reference for "risk characterization" has been added. Also, recommendations regarding the application of adjustment factors for the severity of effect have been added to section 2.1.
Section 3	Revised to some extent; e.g., the BMD is used instead of the BMDL (the uncertainty in the BMD is instead accounted for in the revised uncertainty model described in section 4). Also, the approach for response-adjustment of the RP (if needed) has been modified.
Text box 1	Text box 1 has been revised.
Table 3	The health effect classification scheme has been revised; it has been extended and includes more descriptions.
Section 4	The uncertainty model has been revised including the guidance in Text Box 2. Table 4 has been removed.
Section 5	The risk classification approach/scale has been slightly revised, and also includes statements regarding the uncertainty in the risk classification. This is a result of further development, not due to specific comments. A discussion of the Risk Thermometer in relation to the traditional approach has also been added. Previous

	Table 5 corresponds to Table 4 in revised report. An additional table (Table 5) has also been added to this section.
Figure 3	Figure 3 has been revised; it now consists of three parts 3a, 3b, and 3c, and describes the overall framework.
Text Box 3	A new Text box has been added that discusses the Risk Thermometer in relation to the traditional approach for risk characterization.
Section 6	All examples have been revised due to technical modifications of the approach: 1) use of the BMD instead of the BMDL (for calculating the point estimate of the SAMOE), 2) a modified approach for response-adjustment of the RP (if needed), and 3) revision of the uncertainty model. Changes in the results are due to these technical modifications. In addition, for cadmium the RP has been revised (the new value is regarded to be more appropriate for the target population of interest), and for bisphenol A the RP based on the new EFSA opinion is used (EFSA revised the RP from the draft opinion). Besides updating the text and Tables in section 6, Figure 4 has also been updated. Observe that this is not regarded to represent new graphical front end of the tool. The color bar has been modified mainly since this version is regarded to be more compatible with printing the report in black and white. We have, however, started the process of further developing the graphical front end.
Section 7	Some minor modifications have been made regarding potential future developments of the approach.
Section 8	The conclusion has been updated due to revisions made to the report.
References	A number of references have been added: Baird et al. (1996), ECHA (2012), EFSA (2012), FAO/WHO (2008), Hasegawa et al. (2010), Slob (2007), and WHO (2011). EFSA (2015) has been added instead the previous reference to the draft EFSA opinion on bisphenol A. A reference to the report on the public consultation has also been added (NFA 2015), and Sakhi et al. (2014) has been removed.

3 Common response

Common Response 1: Questions related to how the Risk Thermometer compares to the traditional approach used for risk assessment, and whether or not the suggested approach is more protective/conservative.

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.

<u>Comparison at the level of the severity-adjusted margin of exposure (SAMOE) approach</u>
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 revised Figure 3a). As discussed in modified 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 revised 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 by "*default* HBGV" we mean 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, BMR, in the RP is 10% in the SAMOE approach).

In our opinion, 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 revised 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

revised 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 revised 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 the 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.

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 revised 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 various Risk Classes (see revised 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, 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.

Action

Text box 3 has been added in the revised report.

The summary, section 5, and conclusion has been revised.

Common Response 2: Basis for the selected values of the severity factor (SF).

We agree with the ESFA Scientific Committee that the SF values indirectly correspond to the default uncertainty factors that have been used for many years, and it is noted that e.g., the consideration that a MOE of 10,000 would generally be of low concern for compounds that are both genotoxic and carinogenic is also based on such values (EFSA 2005). Default values are part of today's risk assessment practice in various respects (animal to man extrapolation, LOAEL to NOAEL extrapolation, inadequacy of the database, and sometimes for the severity of effect). Thus, the use of default values (e.g., in a SAMOE or a MOE approach) is not regarded as problematic.

To satisfy objectives with 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 National Food Agency (NFA). Such a practical framework needs to be based on current methodology and risk assessment practice to a high extent, including data requirements and inputs. This implies consideration of MOE or MOE related concepts using 1) an estimate of the human exposure in combination with 2) the use of an exposure reference level derived by state of art methodology including the application of default values (e.g., AFs). The type of framework suggested may be subject to further development, which could make the SF approach less dependent on the use of default values. Besides increasing the number of toxicity-specific subgroups future revisions of the health effect classification scheme may be that the range of x values (i.e., presently x = 0 to 2) and their separation (Table 3) are improved e.g., by considering new (mechanistic) data explaining dose-dependent chain of events within and between individual toxicity-specific subgroups. As discussed in the report (section 7), approaches based on the disability-adjusted life year concept may also be a way forward in the long term perspective.

<u>Detailed description of the current basis for the SF values</u>

As noted in the report, the health effect classification scheme in Table 3 has been developed using the schemes discussed by Burke et al. (1996) and Owen (2002) as a starting point. Burke et al. (1996) suggested the grouping of health effects in three main categories; Category 1, 2, and 3 health effects were regarded as "generally reversible/generally not life-shortening", "may be irreversible/may be life-shortening", and, "irreversible/life-shortening", and they were weighted by factors of 1, 10, and 100 (called Toxicity Severity Indices), respectively. While these factors were not specifically developed for use as in the SAMOE approach they represent previous suggestions (by an ILSI expert panel) regarding the weighting of three broad health effect categories in terms of severity. The resolution in severity was increased in the present work, also resulting in overlap between the three main categories. This development was regarded appropriate because:

1) Specific health endpoints that belong within a given health effect category (e.g., nephrotoxicity) may be quite diverse (e.g., change in kidney marker vs. change in kidney disease).

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 rationale behind the selection of the default SFs is also based on the consideration that an SF = 100 would approximately correspond to the level of protection suggested by EFSA for compound that are both genotoxic 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-individual 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. These additional scenarios were used to define the upper limit of the SF.

Action

Table 3 has been modified in the revised report.

Common Response 3: The case of chemicals that display additional and more severe effects (requiring a larger severity factor) at doses above the critical effect used for establishing the HBGV.

This is an important point. In current practice risk assessments are generally based on one particular (critical) effect, and because of this, it will also be the starting point in the Risk Thermometer. It is noted that the critical effect and RP used as basis will be of importance, in one way or another, regardless of the risk characterization approach used.

However, the example that a chemical may display additional and more severe effects at doses above the critical effect used for HBGV development is interesting. In fact, this is one important basis for the SAMOE approach. Collection of information regarding RPs for say "mild", "moderate", and "severe" health effects (e.g., describing dose related chain of events that differ in severity) may help to revise the default SFs. Conceptually, the SF may be described as 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).

Also, future studies may investigate if RP 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 four of the Risk Classes (see revised Figure 3).

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 classifications. 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.

Action
Table 3 has been revised.
Section 5 has been revised.
Section 7 has been revised.

4 Response to comments from the EFSA Scientific Committee

General response

The Risk Thermometer is a tool for comparative risk characterization across chemicals and health effects while traditional quantitative risk characterization (e.g., as part of scientific opinions) is performed without reference to how the assessment for a given chemical stands relative to the assessment of another chemical. To satisfy objectives with the Risk Thermometer (see objective in the draft/revised 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 National Food Agency (NFA). Such a practical framework needs to be based on current methodology and risk assessment practice to a high extent, including data requirements as well as the use of default values (e.g., adjustment factors, AFs).

These considerations are important drivers for the selection of the severity-adjusted margin of exposure (SAMOE) approach; the methodology behind the Risk Thermometer. The SAMOE is thus not a completely new approach; rather it weights (or integrates) the current output from risk characterization by the severity of effect. Results from the Risk Thermometer represent one basis for further risk management.

Comment 1

The EFSA Scientific Committee expressed a concern regarding the introduction of severity as a parameter for classifying risk (see 3rd paragraph in EFSA comments).

Response

According to Codex (FAO/WHO 2008) risk characterization is defined as: "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".

For chemicals the risk is traditionally described by a MOE, or similar. However, while the MOE indirectly relates to the probability of occurrence (or change in the response) of some health effect the severity of the health effect is generally not accounted for by this measure. See also revised Text box 1 that discusses this issue in more detail. We believe that "probability" (or similar) and "severity" both are important elements of the risk concept, in line with the Codex definition on risk characterization. This consideration is of particular relevance herein since the objective of the Risk Thermometer relates to comparative (quantitative) risk characterization across different health effects in contrast to applications of the traditional MOE approach (as discussed in the general response above). It can be noted

that the BfR also considers “probability” and “severity” in their Risk Profile, which represents a similar tool.

In addition, the relative importance of exposures (at population level) depending on the type of health effects they may cause are issues that ultimately needs to be considered as one part of risk assessment and/or management 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 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 risk analysis process.

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, except some aspects of the severity classification (see revised Table 3 on the latter issue).
- Value-based considerations (risk management): some aspects of the severity classification and the risk classification approach (see revised Table 3 and section 5).

Results from the Risk Thermometer represent *one* basis for further risk management. The approach is 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. For example, this is similar to application of default adjustment factors for inter- and intra-species differences in susceptibility. The Risk Thermometer aims to bridge the three elements of risk analysis (risk assessment, risk management, risk communication).

The summary, section 1, section 2, section 3, Text box 1, Table 3, section 5, and conclusion has been revised to clarify these issues.

Comment 2

The scientific basis for the default severity factors, SFs (see 3rd paragraph in EFSA comments).

Response

See Common Response 2.

Comment 3

The procedure may create the perception that the HBGV is not fully protective with regard to human health (see 3rd paragraph in EFSA comments).

Response
See Common Response 1

Comment 4

The default severity values are also used for the modelling of uncertainty using simulations, which gives a false perception of robustness of the outcome (see 3rd paragraph in EFSA comments).

Response
As described in the revised Table 3, the SF may conceptually be described as 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). Thus, the uncertainty in the SF may be described as a distribution of the ratio between these two (uncertain) reference points. This is similar to suggestions made for how to account for uncertainties in e.g., the default adjustment factor of 10 for animal-to-man extrapolation in a probabilistic setting (e.g., Baird et al. 1996; van der Voet and Slob 2007; Hasegawa et al. 2010; Kalantari et al. 2013). However, specifications of the appropriate uncertainty distributions for AFs (e.g., the standard deviation) 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 on this concept in the first version of the Risk Thermometer but instead use uniform distributions to describe the uncertainty for all parameters of the SAMOE. Future versions of the Risk Thermometer will aim at defining more appropriate uncertainty distributions. Some general improvements of the uncertainty model have, however, been done:

- For the reference point and the exposure the uncertainty analysis is based on data whenever possible. This possibility was not made clear in the previous version of the report.

- To be more consist, a common approach is used for all default values applied (AFs and SFs that are larger than 1). This approach is designed to reflect the extent of application of default values, which generally is regarded to increase the overall uncertainty in the assessment. The uncertainty associated with a default value is assumed to be uniformly distributed, and the lower/upper bounds are based on a quantitative standard (a semi-quantitative approach is used). 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.

Section 4 and Text Box 2 has been revised.

Comment 5

The concept of severity introduces ambiguity and arbitrary weighing factors in the assessment (see 4th paragraph in EFSA comments).

Response

The use of (arbitrary) weighing factors is in fact part of today's risk assessment practice; it is not something that is introduced by the Risk Thermometer. For example:

- EFSA (2005) suggest and additional AF of 100 for compounds that are both genotoxic and carcinogenic; this AF 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 not known).
- While not representing a formalized assessment factor, EFSA (2010) states that a MOE of 10 or greater would be sufficient to ensure that there was no appreciable risk of a clinically significant effect on IQ with respect to neurodevelopmental effects observed in children associated with lead exposure.

These are examples that similar to the default values for the SF represent considerations in the borderline between risk assessment and risk management. Clearly, such considerations are not something that is introduced by the Risk Thermometer; they are part of current chemical risk assessments, in general. Thus, we think that there is no divergence from state of art methodology in this respect. As noted in the general response to the EFSA Scientific Committee a practical framework for comparative (quantitative) risk characterization needs to be based on current methodology and risk assessment practice to a high extent, including data requirements as well as the use of default values. While defaults values are indeed used in the current version, the developed health effect classification scheme is regarded to introduce *less* arbitrariness (and a higher transparency) with respect to the use of default values for the nature/severity of effect.

Also, the EFSA Scientific Committee refers to that the SF assigned to an "increase of kidney cell necrosis" (Category 2c), which is an irreversible effect, is the same as for a "change in estrus cycle" (Category 3b), which is usually fully reversible. The revised version of Table 3 has been clarified in this and other respects. Reversible changes in estrus cycle are covered by "change in hormones" in Category 3a, and Category 3b now includes: "functional effects of changes in estrus cycle". The fact that that Category 3 effects are generally regarded more severe than Category 2 effect is related to value-based considerations. The basis behind the scheme (risk-assessment vs. risk management) is also better described in the revised version of Table 3.

Table 3 has been revised.

Comment 6

The report does not address the potential problem that a chemical may display additional and more severe effects (requiring a larger severity factors) at doses above the critical effect used for establishing the HBGV (see 4th paragraph in EFSA comments).

Response

See Common Response 3.

Comment 7

For effects that are considered to be thresholded, there is no need to introduce severity factors (see 5th paragraph in EFSA comments).

Response

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 is also regarded to correspond to a change in risk/effect, which may be 5 to 10% at the median depending on the study design and endpoint (EFSA 2009; Sand et al. 2011). It is thus regarded that the threshold is somewhere below a *default* 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 severity-adjusted reference point ($SARP_{low}$) below the threshold the NFA regards it still reasonable to require a higher safety margin, for purposes related to quantitative comparisons across health effects, in case of a more severe health effect. For example, in case 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 actual SFs used in the current version of the approach are default values that may be revised in the future.

See also Common Response 1. Text box 1 has been revised.

Comment 8

Additional considerations may be given to the steepness of the dose-response curve (see 5th paragraph in EFSA comments).

Response

Yes, this is a good idea. We agree that the steepness or shape of the dose-response curve is of importance. It should be noted, however, that this is not accounted for at the level of quantitative risk characterization in current practice; e.g., the steepness of the curve is not part of a MOE calculation. Similar to the MOE, the outcome of the SAMOE and Risk Thermometer represents one basis for further risk management. However, the possibility to account for the shape of the dose-response curve (or the uncertainty thereof) could be investigated as the Risk Thermometer is further developed.

Since national authorities like the Swedish National Food Agency (NFA) rarely perform detailed hazard characterizations themselves, results available from risk assessment reports by international health agencies are important sources. It may be noted that the level of detail in such reports with respect to quantitative dose-response information may vary, and the type of RP used in international assessments (e.g., BMDLs, NOAELs, or LOAELs) may differ on a case by case basis. Consequently, a practical approach for comparative (and quantitative) risk characterization currently needs to be operable in the absence of detailed dose-response information (e.g., regression parameters providing information on the slope of the curve) as well as allowing diversity in RPs.

Comment 9

Whether a "mild" effect affecting a large number of individuals is more important compared with a "severe" effect affecting only a few individuals is a risk management and a societal issue and therefore is not within the remit of risk assessors (see 5th paragraph in EFSA comments)

Response

Yes, we agree that these are aspects outside the scope of risk assessment. The consideration of a "mild" versus a "severe" critical effect is part of the Risk Thermometer, since the element of severity is included. However, who (children, adults etc.) and how many humans that are affected is regarded as question of risk management alone, and is not part of the Risk Thermometer. As noted in the report (e.g., the summary of the report) the results from the Risk Thermometer 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 consideration, are not explicitly included. The consideration of such aspects needs to be made separately. However, the Risk Thermometer may be used to derive scenarios that for example describe the situation for various target populations or consumer groups as a basis for risk management.

The summary, sections 3, section 5, section 6, and conclusion has been overviewed in this context, and minor revisions have been made.

Comment 10

The margin of exposure (or margin of safety) approach, comparing a reference point (or a HBGV) with an estimated exposure for the target population, already provides a tool for setting priorities for applying risk management measures without the need to introduce severity considerations (see 6th paragraph in EFSA comments)

Response

If this is the case, priority setting (using the MOE or MOS) will indirectly be based on the concept of "probability", only (see also response to EFSA Comment 1 and response to EFSA Comment 7 regarding thresholds). However, the Risk Thermometer must also account for the nature of the health effect since this is a consequence of the objective, which is to develop a tool for comparison of chemical risks (see objective in the report); "comparison of chemicals risks" implies comparison *across* chemicals and also *across* health effects. The Risk Thermometer is thus a tool for comparative (quantitative) risk characterization across chemicals and health effects; it account for both the concepts of "probability" and "severity". See also revised Text box 1 that discusses this issue in more detail.

It can also be noted that NFA risk managers apparently do not agree with EFSA Comment 10 since the mandate was given to develop a tool for quantitative risk characterization across health effects that can be used for prioritizing and communicating food related health risks. As discussed previously, the relative importance of exposures (at population level) depending on the type of health effects they may cause are issues that ultimately need to be considered as one part of risk assessment and/or management 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 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.

Text box 1 has been revised.

5 Response to comments from the Finnish Food Safety Authority (EVIRA)

Response to general comment

Yes, we agree that the Risk Thermometer enables prioritization of risk mitigation measures, and can be useful in risk communication between the risk assessors and risk managers.

Comment 1

A major proportion of the tool concentrates on hazard assessment, whereas exposure assessment is described only briefly. It would be useful to also explain the uncertainties of exposure assessment in the report and possibly to use some uncertainty factor(s) for e.g. method used for exposure assessment.

Response

By tradition, uncertainty/adjustment factors have mostly been discussed with respect to the hazard assessment. This may be a somewhat "one-sided" consideration. Uncertainties with respect to exposure assessment are more commonly considered in recent years due to increased discussion of probabilistic approaches. As discussed in the future developments (section 7 of the report) the SAMOE approach 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 more traditional margin of exposure approach, which could be extended to the SAMOE.

In the revised version of the report the uncertainty model has been modified, and more emphasis is placed on using data driven inputs for the exposure (and the reference point) when this is available.

Section 4 has been revised (see also our response to EFSA Scientific Committee Comment 4).

Comment 2

Page 6, Sammanfattning: "...ju allvarligare hälsoeffekten bedöms desto större säkerhetsmarginalen anses behövas." This is only partly true. Any adverse effect or impact of a chemical should be avoided.

Response

Yes, this was written to give a simple description of the SAMOE approach in Swedish.

The Swedish summary has been slightly revised.

Comment 3

When the risk assessor reports the results to the risk manager, the risk assessor should also report the details behind the result: is the final result rather due to amount of the exposure, properties of the chemical or quality of the original data. These details help risk manager to target risk mitigation measures correctly. The correct risk mitigation measure may be for instance an attempt to reduce intake of chemical in population. Problems in data quality may cause uncertainty in results and high risk result. This may be signal for need for further studies.

Response

We agree. This is an important point. The consequence of the final results (i.e., classification in Risk Class 1, 2, 3, 4 or 5) may depend on various issues.

In the revised version we have included a discussion on this in section 5. Also, the numerical outputs described in section 6 have been updated and include information that can help to explain the impact of application of default factors (AFs and SF) on the SAMOE value (presented as a MOE/SAMOE ratio).

Section 5 (last paragraph) and section 6 (including Table 6A-6E) have been revised.

Comment 4

The Risk Thermometer uses a standardization of benchmark levels to BMDL10. The equation 3 (on p.17) appears to assume linear change in the response between, say, BMDL5 and BMDL10. We would ask for more clarification on whether this assumption is valid for different types of hazards. If the response is nonlinear, doesn't equation 3 lead to an erroneous factor in the final assessment?

Response

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 $BMDL_{10}$ was considered as the main reference, partly since this BMDL is used most frequently in current practice (see also revised Text box 1). Since national authorities like the Swedish National Food Agency (NFA) rarely perform detailed hazard characterizations themselves, results available from risk assessment reports by international health agencies are important sources. Sometimes the response associated with the BMDL is different from 10% (and if so, generally a lower than 10%), and NOAELs, or LOAELs may also be applied. Consequently, a practical approach for comparative (and quantitative) risk characterization needs to allow diversity in the RPs.

The BMR-adjustment was introduced to reduce impact in the case of BMDLs based on response levels different from 10%. We agree that the relevance of a linear assumption may

differ on a case by case basis. The approach has therefore been modified so that more options are allowed. In the revised report an adjustment factor ($AF_{BMR} > 1$) is applied in case of a LOAEL, and also in case of a BMD associated with a BMR different from 10% (if this is regarded to be needed). As a default $AF_{BMR} = 3$ is used for a LOAEL (downward adjustment), and also for a BMD_{01} (upward adjustment). A factor of 3 - 10 is recommended by ECHA (2012) for adjustment of a LOAEL. This modification was also performed due to comments from the Swedish Chemicals Agency. Moreover, in the revised version the BMD rather than the BMDL is used for estimating the point estimate of the SAMOE. This is a consequence of modifications made to the uncertainty model; all uncertainties are now consequently accounted for in the same step (see revised section 4).

Section 3 has been revised with respect to the response-adjustment.

Comment 5

It is an excellent idea to classify different health responses based on the relative harmfulness of the effect. However, the factors used to calculate the SF would need more details so that different risk assessors would use the same factor for the same chemical.

Response

More descriptions/clarifications have been added in the in the revised version of the scheme, and it has also been extended. Also, practical experience may help to identify situations were more guidance is needed to reduce discrepancies as a result of subjective judgment.

Table 3 has been revised.

Comment 6

Also it is worth noting that a chemical may have several types of health effects, and the SF should be calculated for all of them if there is quantitative data. The health effect with the lowest BMDL (which is usually used in determining the TDI or TWI levels) is not always the most severe. For example cadmium has been linked to estrogenic effects in some studies and it is considered a group I carcinogen, which are both more serious effects than the kidney enzyme marker level change. The RP / (AF x SF) may therefore vary for the same chemical depending on which endpoint is considered.

Response

See Common Response 3

Comment 7

If understood correctly, SAMOE is based on systemic effects. However, in Table 3 in page 23, local irritation or hyperplasia of epithelial or mucosal surface is an effect that leads to

health effect classification. Even though local effects may also be important, the extent of their effect is based on concentration (mg/l) rather than on dose (mg/kg bw/day). Therefore, it is proposed that local effects are not taken into account in determining the hazard class.

Response
Yes, we agree. In the revised scheme this category has been clarified and modified. It is now called "Early clinical signs of toxicity" and an example of this is "irritation (e.g., redness, salivation) of epithelial or mucosal surface in contact with chemical". The severity factor for this category is set to 1 in the revised version.

Table 3 has been revised.

Comment 8

In table 3, it is mentioned that change of clinical chemistry parameter could lead to class 2a in hazard classification. However, in toxicological tests there are almost always some deviations in clinical chemistry parameters. If there is no link to respective target organ toxicity, these effects are often disregarded. Therefore, hazard classification based only on clinical chemistry is not feasible.

Response
Yes, we regard that the relevance of deviations in these parameters (as well as other biochemical parameters) depends on various aspects, e.g., the specific endpoint including the degree of deviation/change. To be considered in the context of the SAMOE approach effects must be regarded to have toxicological relevance (critical effects or similar), and information on dose-response needs to allow the derivation of an RP. We regard that this will rule out clinical chemistry parameters that are toxicologically irrelevant or show minor deviation and/or unclear dose-responses. This is clarified by adding the term "marker" so that this subcategory now reads "change in clinical chemistry parameters/markers".

Table 3 has been revised.

Comment 9

To assess the uncertainty related to toxicity, significant variation in the metabolism of xenobiotics is found between humans of different genetical background. Mechanism of metabolism for the xenobiotic should be known so as not to underestimate the risk to the sensitive individual. This comment is not directed only to the Risk Thermometer but to the toxicity assessments worldwide.

Response
Yes, this is generally not accounted for in today's risk assessments. We think it represents an issue for further consideration.

6 Response to comments from the Swedish Chemicals Agency

Response to general comment

We agree with the Swedish Chemical Agency that the suggested approach might be useful for chemicals more generally (and not only food related chemicals), and that the approach contributes to providing a higher transparency regarding the choice of default/standard factors used in risk assessment (bedömningsfaktorer) and their size. The Swedish Chemical Agency's suggestions regarding development of the concept with the severity factor are addressed below (see Comment 2). We also think that attempts to quantify the overall uncertainties in risk characterization, as well as presenting it to risk managers and the public, is of value.

Comment 1

Choice of reference point; even though the case of a LOAEL is accounted for in the uncertainty model, it is suggested that an AF of at least 3 is applied to the LOAEL in line with REACH methodology.

Response

Yes, we agree. In the revised version an AF is applied in the case of a LOAEL. A factor 3 is used as a default.

Section 3 has been revised in this context.

Comment 2

The severity factor; for "cancer" it is suggested that it would be appropriate to differentiate between genotoxic and non-genotoxic mechanisms, and it is noted that mutagenicity is not included in Table 3. It is also suggested that "sensitization" is mentioned even though it may be included in "Immunotoxicity 2b".

Response

The health effect classification scheme has been revised and extended in the final version of the report. However, we do not differentiate between genotoxic and non-gentoxic mechanisms for cancer in the current version of the Risk Thermometer since we think that the issue of threshold vs. non-threshold effects may extend beyond the case of cancer. However, an additional severity level "3a) genetic toxicity *in vivo*" has been added to the scheme. Also, the description for immunotoxicity 2b has been modified to also include "sensitization".

Table 3 has been revised.

Comment 3

Comment on the uncertainty analysis.

Response

We also think it is positive that the overall uncertainty involved in the risk assessment is quantified and presented for risk managers and the public. While the approach used in the current version of the Risk Thermometer may be further refined, we regard that this type of exercise e.g., helps to better realizing that the overall uncertainties involved sometimes may be quite significant.

Comment 4

Risk Thermometer examples. Even though it is stated in the report that these examples concern adults it would be valuable to also shown result for the risk groups.

Response

In the revised report examples have been updated due to minor technical modifications of the SAMOE approach and since the uncertainty model has been revised. However, the examples still concern the average individual both in terms of exposure and susceptibility, and represent reference scenarios. Adults are considered since exposure data relates to adults, and since the examples do not reflect formal application of the approach we decided not to derive results for particular consumer/risk groups. Briefly, however, application of an additional AF = 10 to account for sensitive individuals would reduce the SAMOEs by a factor 10. For lead, dioxin, and cadmium this would result in an increase of the Risk Class by one level.

Section 6 has been revised.

7 Response to comments from the UK Food Standards Agency

Comment 1

For genotoxic carcinogens, the approach is essentially what we currently do based on EFSA Scientific Committee guidance and WHO principles. Ranking is straightforward and informs risk management priorities.

Response

Yes, we agree.

Comment 2

The new approach relates to approaches for substances in food that are not genotoxic. Currently if we were asked to rank such substances we would say there is no concern if exposure is below a health-based guidance value. Risk could be ranked based on exceedance of the health-based guidance value if it occurs, and this is also understood by risk managers.

Response

Yes, currently we also do this. Essentially, the difference with the Risk Thermometer is that the consequence (type of health effect) associated with exceeding the HBGV is also accounted for. The relative importance of exposures (at population level) depending on the type of health effects they may cause are issues that ultimately need to be considered as one part of risk assessment and/or management 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 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.

Comment 3

We consider that the report proposes a more conservative approach to non-genotoxic substances which we believe would lead to conclusions of concern about many authorised chemicals in food (food additives, pesticides, vet meds, food contact materials, etc). If that is the case, we consider that such conclusions would be subject to scientific and regulatory challenge, and not risk-proportionate.

Response

Briefly, introduction of the element of severity is regarded to make the severity-adjusted reference points (SARPs, see revised Figure 3) formally more comparable across health effects than a *default* HBGV. This is the reason for the application of severity factors (SFs),

but may indirectly make $SARP_{low}$ (see revised Figure 3) theoretically more protective/conservative than a *default* HBGV (for some non-genotoxic chemicals for which the SF is set to values larger than 1). At the level of the risk classification the Risk Thermometer is regarded not to be fundamentally more conservative than the traditional risk assessment approach. We do not think that Risk Thermometer would systematically lead to conclusions of concern about many authorized chemicals in food, while the traditional approach would not lead to such concerns. Experience of using the Risk Thermometer will be helpful in providing more insights in this context.

See Common Response 1 for more details.

Comment 4

The report notes that the approach is currently limited to chemical risks associated with chronic exposure. It mentions that it could be extended to cover acute effects of chemicals as well as risks associated with microbiological agents, but it was not clear how this might be achieved.

Response

Potential extensions of the concept, and approaches for linking chemical and microbiological risks are briefly discussed in section 7 of the draft (and the revised) report. In the revised report the type of statement discussed in Comment 4 above is given in the conclusion. It is clarified that this may be a future challenge rather than that we already now have detailed suggestions for how development of a more generalized framework for comparative risk characterization may be achieved.

The conclusion has been revised in this context.

8 Response to comments from Nestlé

Comment 1

It may be a useful approach to evaluate, compare and prioritize compounds across different categories, including genotoxic carcinogens and mixtures using the margin of exposure. It sounds reasonable to start from the toxicity reference value, apply a severity factor depending on the hazard identified and compare it to the exposure.

Response

Yes, we agree.

Comment 2

It would be interesting to see how it works for compounds with several sources of uncertainties coming both from the tox database and exposure. At least for the examples given it looks OK. The application of several uncertainty factors may make it over-conservative, but this maybe has to be shown in practice.

Response

See Common Response 3 for the case of several potential reference points (RPs) and critical effects. The uncertainty model has also been revised and more emphasis is now placed on using data driven inputs with respect to uncertainties in the exposure and the reference point when this is available (see revised section 4). Moreover, see Common Response 1 for issues related to whether or not this approach is more protective/conservative relative to the traditional approach.

Comment 3

One single SAMOE value does not tell you where the uncertainties and gaps are (compounds with poor database), and specialists would have to go back to the data used.

Response

See Common Response 3 that addresses the case of several potential RPs and critical effects.

Comment 4

For communication to consumers the thermometer may be a useful tool, but also other tools, perhaps like a traffic light system could be considered.

Response

Yes, this is a possibility. We are in the process of further developing the graphical front end (the consumer oriented perspective).

Comment 5

The BfR approach is also mentioned, and it seems that the matrix the BfR use looks a bit different, more qualitative, and they don't come up with a single 'value'.

Response

Yes, we consulted the BfR in the beginning of this project. We decided to just have one scale (combing the concepts of "probability" and "severity") to better facilitate direct comparison between results (e.g., comparison of Risk Thermometers for different compounds).

9 Response to comments from the Swedish Food Federation

The Swedish Food Federation stresses that the level of detail in the draft report is such that it is hard to access without specific expertise in the area. The public consultation has been communicated across Europe. Thus, several parties have had the opportunity to provide comments.

The Swedish Food Federation is positive to the principle of developing a Risk Thermometer tool for improving the communication regarding food related risks. We think that the tool for example may enable differentiation between potential risk situations that are reported in the media. We agree with the Swedish Food Federation that the consumer oriented perspective (the graphical front end) should be carefully designed and appropriately used. We are currently in the process of further developing that part of the Risk Thermometer.

The Swedish Food Federation thinks it is important that the suggested approach is in line with the risk assessment practice at the European Food Safety Authority (EFSA) and that the Risk Thermometer uses EFSA's approach as a starting point (which is also the case). The Swedish Food Federation also stresses that use of the Risk Thermometer must not result in that health risk are assessed differently (more or less conservative) between the National Food Agency (NFA) (i.e., Sweden) and the EFSA.

To satisfy the objectives with the Risk Thermometer the challenge has been to develop a framework for comparative risk characterization that efficiently can be integrated in today's risk assessment, risk management, and risk communication workflow at the NFA. It is regarded that such a practical framework needs to be based on current methodology and risk assessment practice to a high extent, including data requirements and inputs. See Common Response 1 for further details regarding how the suggested approach relates to the traditional approach.

10 Response to comments from Professor Robert Nilsson

General response

The provided document discusses risk assessment and chemical risks quite generally. Our response will mainly focus on parts that specifically address the draft report on the Risk Thermometer.

The document received mainly argues that the Risk Thermometer/SAMOE approach is a highly conservative (protective) approach. At a few places it is even suggested that the Swedish National Food Agency (NFA) may ban products if the SAMOE value is low. Observe that The Risk Thermometer represents one tool for further risk management, just like the traditional approach for quantitative risk characterization. It is not a tool for banning products.

We generally refer to Common Response 1 regarding how the suggested approach compares to the traditional approach: our approach is in fact not considered to be highly conservative. More specifically, comments in the provided document resulting from comparison of the MOE and SAMOE are problematic. The MOE (indirectly) accounts for the element of "probability", while the SAMOE accounts for both "probability" and "severity" (see revised Text box 1 for more details on this issue). Introduction of the element of severity is regarded to make the severity-adjusted reference points (SARP/s, see revised Figure 3) formally more comparable across health effects than a traditional health-based guidance value (HBGV), or similar. This is the reason for the application of SFs; SAMOEs are regarded to be more comparable *across* health effects compared to MOEs.

Importantly, when considering whether or not a particular SAMOE is high or low (in an "absolute" context) reference should be made to the risk classification scale (Risk Class 1 through 5), not by comparing it to a traditional MOE value. For example, a SAMOE = 1 (which lies in the border between Risk Class 2 and 3) corresponds to a MOE = 10,000 for a genotoxic carcinogen (if the reference point, RP, is based on animal data). The level of concern according to the SAMOE is not necessarily higher just because the value (relative to a traditional MOE) is lower. In the revised report it is better clarified how the Risk Thermometer compares to the traditional approach.

Text box 3 has been added. The summary, Text box 1, section 5, and the conclusion have been revised.

Comment 1

Section "Allmänna synpunkter"

Response
We agree that quantitative approaches for risk assessment provide results that are appropriate for use in the process of decision making (risk management). Related to issues described in the last paragraph, the draft report has in fact been communicated across Europe. Thus, several parties have had the opportunity to provide comments.

Comment 2
Section "Inledning"

Response
This section suggests more information on WHO risk assessment principles in the summary since it is suggested that the Swedish society in generally is uniformed with respects to risk assessment. The draft report serves as the scientific and value-based foundation for the Risk Thermometer, and is not directed to the general public; other descriptions/reports may later satisfy this aspect. The Swedish summary is, however, written for a broader group, but we do not think it should be made more complicated by including the WHO definition on risk assessment.

The comments in this section also point out that the risk assessment and risk management elements of the Risk Thermometer should be better clarified. We agree that this is an important point.

The summary, introduction, Table 3, section 5, and conclusion has been revised to better clarify the risk assessment and risk management elements of the Risk Thermometer.

Comment 3
Section "Olika modeller för riskuppskattning"

Response
This section summarizes parts of the introduction in the draft report, discusses general principle for traditional risk assessment, and generally describes the principle behind the SAMOE. We have no comments to this section, except that while the assumption of a linear dose-response relationship in the low-dose region in the case of gentoxic carcinogens (e.g., used by the USEPA) indeed has a scientific basis, it is also a very pragmatic approach. Since we generally do not know the slope of this line, low-dose linear extrapolation is generally regarded to provide "upper bound estimates" of risk, not best estimates (see section 2.1 in the report).

Comment 4

Section ”Allmänt om utvärdering av icke-genotoxiska och genotoxiska agentier”, second paragraph.

Response

This section suggests that it is not mentioned in the report how to handle non-genotoxic carcinogens. In fact, the report concerns chemicals in food quite generally, including both genotoxic and non-genotoxic compounds.

Comment 5

Section “SAMOE”

Response to 1st paragraph

It is regarded that the “SAMOE-system” is rational, but also very technical. In principal, our approach differs from traditional quantitative risk characterization by the systematic use of an assessment factor for the severity of effect (the severity factor, SF). We do no regard this to be much more technical than the traditional approach. See Common Response 2 concerning the rationale behind the severity factors used. Observe that the suggested approach concerns chemicals in food generally (including genotoxic carcinogens). Also, it is suggested that our model is similar to Owen (2002). This comment is misleading. For development of the health effect classification scheme (Table 3), Burke et al. (1996) and Owen (2002) have been used as a basis. Burke et al. (1996), in particular, provided a starting point for severity classification, and Owen (2002) provided to some extent a starting point for adding descriptions of health effect categories in the scheme. Our approach for risk characterization is, however, not based on Owen (2002), and we do not think that our approach should apply to non-genotoxic compounds, only; for genotoxic compounds it becomes is in fact equivalent to the traditional approach applied for such compounds (e.g., see revised Figure 3a).

Response to 2nd paragraph

See revised Table 3 for more description on the design of the classification scheme (the scheme has been extended in the revised version of the report). Regarding the suggestion that it may not always be appropriate to add an extra safety margin of 100 for severe effects: observe that while a NOAEL may correspond to a statistically insignificant increase in risk it is not a risk-free dose in terms of benchmark response (BMR, the response associated with a BMDL derived from dose-response modelling). Based on overview of data from the U.S. National Toxicology Program the BMR at the NOAEL corresponds to a 10% risk at median (Sand et al. 2011). Also, as noted in Common Response 2 as well as in the draft report, the SF of 100 for compounds that are both genotoxic and carcinogenic imply approximately the same level of protection as suggested by EFSA, and it is also indirectly in line with the EPA target range for risk management (e.g., see revised Figure 3a). Consequently, there is no extra factor

of 100 that has been added in this context (if we understand this comment correctly). We think that the approach indeed is applicable for inorganic arsenic, and other carcinogens.

Response to 3rd paragraph

The approach concerns non-cancer as well as cancer effects (with or without genotoxic mechanisms). Both human and animal data is used for risk assessment, derivation of health-based guidance values (HBGVs), reference points (RPs) etc. The Risk Thermometer is not different in this respect. The nature of the data used for RP derivation (e.g., animal vs. human) guides the application of adjustment factors (AFs) to the RP (see Table 2 in the report), and the severity classification (Table 3) concerns the health effect used as basis for RP derivation. The severity classification does not depend on whether the RP is based on human or animal data; this is accounted for by the AFs.

Response to 4th paragraph

What determines the severity classification depends on the health effect associated with the critical effect (not the type of chemical). It is realized that a single chemical may be able to cause different effect, but in line with current practice the assessment is based on the critical effect. See guidance for how to set the severity factor in revised Table 3. Further developments, in general, may result in approaches (for practical use) that accounts for the effects that may be caused by a chemical in a more multidimensional context. See also Common Response 3 that discusses this issue further.

Comment 6

Section "Tillämpning av SAMOE på toxiska ämnen i mat och dryck - några exempel"

Response

See the general response (to comments from Professor Robert Nilsson) that generally addresses the comparisons of SAMOE and MOEs in this section.

The fourth paragraph of this section suggests that results under the SAMOE approach, with respect to a number of examples (which are later presented), are inappropriate. As described below, this conclusion is flawed.

Inorganic arsenic: The BMDLs derived by EFSA concern a 1% cancer risk, not 10% as written in the comments. It is stated in the comments that the BMDL interval is not "reasonable", and it is then argued that the SAMOE-system overestimates the situation. If the BMDL interval indeed is "unreasonable" this will make any assessment "unreasonable". However, we regard that low safety margins in the case of arsenic do not imply that the risk situation is extremely overestimated. It may rather imply that arsenic is a priority relative to other compounds; the Risk Thermometer is *one* tool for risk management.

Ethyl carbamate: It is concluded that "Systembolaget" has to get rid of many of their products because SAMOE values of e.g., 50, which by the way classify in Risk Class 1 ("no concern").

This conclusion is flawed. Importantly, the Risk Thermometer represents one tool for further risk management.

Other compound: Similar to the case above SAMOE values (e.g., of 15 for NNK) classifying in Risk Class 1 are discussed to be problematic, which would rather indicate the opposite.

Generally speaking, however, we agree that some naturally occurring compounds, which are partly discussed in this section of the comments, may have small safety margins. The idea with the Risk Thermometer is to account for the greater context, which is not performed in today's quantitative assessment; accounting for both "probability" (or similar) and "severity". Accounting for the greater context, may lead to better differentiation regarding the impact and significance of various types of chemical exposures. Also, as noted in the last paragraph of Common Response 1, several aspects besides the Risk Class may be relevant in a broad risk management perspective. For example, Risk Class 1 and 2 substances may still have priority if their presence in foods is highly unacceptable, and conversely, Risk Class 4 and 5 substances could have less priority if they are present in foods due to natural reasons, only.

Comment 7

Section: "Riskvärdering av carcinogener grundad på molekylärepidemiologiska data, en bortglömd aspekt"

Response

This section summarizes that safety margins for Swedish "snus" with respect to cancer are comparable to that for other pollutants in food, and even larger than that for some other compounds. We have no specific comments to this since it is not regarded relevant for issues specifically associated with this consultation.

Comment 8

Section "SAMMANFATTANDE KOMMENTARER"

Response to 1st paragraph

This section initially states that the suggested "SAMOE-methodology" is logical, and part of a good tradition where management decision are based on quantitative risk assessments, which may minimize arbitrarily and politically motivated actions in Sweden. We agree with this comment.

Response to 2nd paragraph

This section raises a concern that risk assessments may become reduced to a mathematical exercise, only. However, as noted above, the first paragraph suggests on the other hand that there are advantages with quantitative approaches. Even so, we agree that this is an important point to keep in mind when using the Risk Thermometer or any other quantitative tool for risk

assessment; the Risk Thermometer represents *one* tool for risk management. Also, it is suggested that the objective has not been satisfied, since the draft report (or methodology) is difficult to comprehend (for the public?). As described in the introduction, the report is concerned with the underlying elements of the Risk Thermometer, serving as its scientific and value-based foundation. The draft report is not directed to the general public; other descriptions/reports may later satisfy this aspect. Also, a number of revisions have been made due to all comments received which we think has helped to improve the Risk Thermometer report.

Response to 3rd paragraph

While this section regards it to be reasonable to account for the element of severity, it also suggests that arbitrary adjustment factors are used in the approach. See our response to EFSA Comment 5 on the issue of arbitrary factors used in risk assessment. We also refer to Common Response 2 regarding the basis for the severity factors used. This paragraph also argues that safety margins become too high when using the suggested approach. As described in responses to the more specific sections above (also accounting for the examples provided) this is not regarded to be the case. As also described previously, there is not extra factor of 100 applied in the case of genotoxic carcinogens. See Common Response 1 regarding how the suggested approach compares to the more traditional approach.

Response to 4th paragraph

It is suggested that application of the Risk Thermometer will have negative effects for food production that may ultimately lead to that certain products are banned. This connects to the issue of safety margins addressed in the paragraphs above. As already stated elsewhere, the Risk Thermometer represents one tool for risk management, it is not a tool for banning products.

As indicated in the summary and the conclusion of the Risk Thermometer report, 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. Also, 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. It is within the responsibilities of the NFA to work for such improvements.

11 Response to comments from Svensk Dagligvaruhandel

Svensk Dagligvaruhandel is skeptical to that the type of risk assessments described (i.e., comparative risk characterization using the Risk Thermometer) can be done. They point out that there is a risk for over-simplification which can be misleading, for example occupational aspects are not accounted for.

We would like to highlight that the approach suggested may actually be regarded to be less simplified than the traditional approach for quantitative risk characterization, since the latter does not generally account for the type of health effect the risk assessment is based on. If there is a certain probability of occurrence of some health effect, the significance of this will depend on the nature of the health effect. The suggested approach includes this important dimension. Besides this, the methodology behind the Risk Thermometer is in principle the same as the traditional approach. See Common Response 2 for the rationale behind the severity factors currently used.

The exposure from foods is within the responsibilities of the National Food Agency (NFA), not occupational exposures. The "exposure" is one of the parameters of the Risk Thermometer, and in principle it may be the exposure from sources other than foods. Future initiatives may address risk comparisons more generally.

We agree with Svensk Dagligvaruhandel that chemical risks are difficult to communicate and that it may also be a charged/sensitive issue. The NFA is, however, required to assess, rank/prioritize, and communicate chemical risks. The consumer and the media also need to prioritize their views on chemical risks. These issues do not disappear just because there is no Risk Thermometer, or similar. In the light of this reality, the NFA regards it as an improvement that the organization has developed a first version of a more systematic strategy for risk comparison. This is also expected to reduce inconsistencies between assessments, and introduce a higher transparency regarding how different aspects are allowed to impact, quantitatively, in the process of risk analysis. The Risk Thermometer does not replace risk management; it proves *one* basis for further risk management. See also the last paragraph in Common Response 1.

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Appendix A: Original comments

Summary of the comments made by the EFSA Scientific Committee during its 71st plenary meeting on the draft report "The Risk Thermometer" presented by Dr. Salomon Sand[1]

Parma, 26 February 2015

Dear Dr. Sand, dear Salomon

Thank you again for your presentation of the draft report "The Risk Thermometer" during the 71st plenary meeting of the EFSA Scientific Committee. Communication of risks associated with food consumption is one of the key activities of EFSA and the EFSA Scientific Committee is always keen of reviewing new approaches and tools brought to its attention. As agreed, please find below the comments that the EFSA Scientific Committee would like to bring to the attention of the authors of the report.

The Risk Thermometer aims at communicating levels of risks to the "customers" by the Swedish National Food Agency. The intention is to develop a tool that may be used for comparing food related risks. The systematic use of this new approach should allow for the grouping of substances used in food based on their risk level, expressed on a common scale, with the possibility to prioritise risk management measures (e.g. food controls) to substances associated with a high risk. The proposed risk ranking uses severity factors, ranging from 1 to 100, in addition to the traditional uncertainty factors used to establish Health Based Guidance Values (HBGV). The rationale for this is that the size of a margin between a HBGV (now called population-adjusted reference point (PARP)) and the estimated exposure of consumers to a chemical which is considered acceptable is claimed to be dependent on the severity of the critical health effect. The resulting severity adjusted value is then used to classify chemicals into 5 risk categories.

The EFSA Scientific Committee wishes to express its concern regarding the introduction of severity as a parameter for classifying risks. The scientific basis for the default severity factors (10^x) proposed in the above-mentioned report is not clearly presented (the values proposed are mostly the default uncertainty factors (3.16, 10) that have been traditionally used in chemical risk assessment for at least the last five decades). Starting from the PARP (equivalent to the HBGV), these default values are used to establish severity adjusted reference points (SARP). This procedure may create the perception that the HBGV is not fully protective with regard to human health. Furthermore, the default severity values are also used for the modelling of uncertainty using simulations, which gives a false perception of robustness of the outcome: if variability of measured data is worth modelling, one could question the validity of translating parameters that have been determined qualitatively in quantitative terms (lower bound and upper bound). In other words, the fact that point estimates /default values are used as the basis of a probabilistic approach is questioned. Although the approach is presented as intended for chronic toxicity, the Scientific Committee notes

[1] This set of comments was drafted by the members of the EFSA Scientific Committee: Prof. Jan Alexander, Dr. Alicja Mortensen, Dr. Josef Schlatter, and by EFSA Staff of the Scientific Committee and Emerging Risks Unit: Mr. Bernard Bottex and Dr. Jean Lou Dorne

that some of the health effects listed in Table 3 of the report are acute effects, and that the bladder and pancreas as target organs are not listed in table 3.

The EFSA Scientific Committee has therefore reservations towards the approach proposed in the above mentioned document because the concept of severity introduces ambiguity and arbitrary weighing factors in the assessment. As an example, the severity factor assigned to an increase of kidney cell necrosis, which is an irreversible effect, is the same as for a change in estrus cycle, which is usually fully reversible. Further, the report does not address the potential problem that a chemical may display additional and more severe effects (requiring a larger severity factors) at doses above the critical effect used for establishing the HBGV.

The EFSA Scientific Committee is of the opinion that, for effects that are considered to be thresholded, there is no need to introduce severity factors. It is common risk assessment practice to apply an additional uncertainty factor to derive a HBGV when there are large uncertainties around the critical effect (e.g. deficiencies in the data-basis). Moreover, additional considerations may be given to the steepness of the dose-response curve when exposure is expected to be in the range of the HBGH to inform risk managers. Consideration of whether a "mild" effect affecting a large number of individuals is more important compared with a "severe" effect affecting only a few individuals is a risk management and a societal issue and therefore is not within the remit of risk assessors.

The EFSA Scientific Committee finally stresses that the Margin of Exposure (or Margin of safety) approach, comparing a reference point (or a HBGV) with an estimated exposure for the target population, already provides a tool for setting priorities for applying risk management measures without the need to introduce severity considerations.

The EFSA Scientific Committee thanks again the Swedish National Food Agency for this opportunity to comment on the draft report "The Risk Thermometer".

Best regards.

Bernard Bottex

Secretariat of the EFSA Scientific Committee

cc: EFSA Scientific Committee, Tobin Robinson, Juliane Kleiner, Marta Hugas, Daniela Maurici, Jeff Moon.

Evira

Research and Laboratory Department
Risk Assessment Research Unit

Pvm/Datum/Date
2015-02-05

Dnro/Dnr/DNo
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SLVs Diarienumret 1352/2014

Evira's comments on Risk Thermometer draft report

Please find enclosed comments from Finnish Food Safety Authority Evira on Risk Thermometer draft report.

Risk Thermometer is a tool where one can assess chemical risks quantitatively. The Risk Thermometer provides a tool to compare risks and enables priorisation of risk mitigation measures. Thus risk mitigation measures can be targeted appropriately and effectively. The tool can be useful in risk communication between the risk assessors and risk managers. It uses (previously determined values for) exposure of the consumers and a modified approach for the assessment of the relative toxicity of the chemical.

The advantage of the SAMOE approach is that it enables a continuous scale for risk chemicals (SF = 100…10,000), based on properties of a chemical and on the severity of the end point.

Detailed comments

A) The concept behind the severity-adjusted margin of exposure (SAMOE), and its role as a more comparative measure than traditional margin of exposure related metrics including the assessment of exposures in relation to health-based guidance values (section 3 in the report).

- A major proportion of the tool concentrates on hazard assessment, whereas exposure assessment is described only briefly. It would be useful to also explain the uncertainties of exposure assessment in the report and possibly to use some uncertainty factor(s) for e.g. method used for exposure assessment.

- Page 6, Sammanfattning: "...ju allvarligare hälsoeffekten bedöms desto större säkerhetsmarginalen anses behövas." This is only partly true. Any adverse effect or impact of a chemical should be avoided.

  The Risk Thermometer is a tool for risk assessors. The risk assessor gets a numerical value that describes the severity of the risk. Based on the result, the risk

manager can priorize risk mitigation measures.

- When the risk assessor reports the results to the risk manager, the risk assessor should also report the details behind the result: is the final result rather due to amount of the exposure, properties of the chemical or quality of the original data. These details help risk manager to target risk mitigation measures correctly. The correct risk mitigation measure may be for instance an attempt to reduce intake of chemical in population. Problems in data quality may cause uncertainty in results and high risk result. This may be signal for need for further studies.

- The Risk Thermometer uses a standardization of benchmark levels to BMDL10. The equation 3 (on p.17) appears to assume linear change in the response between, say, BMDL5 and BMDL10. We would ask for more clarification on whether this assumption is valid for different types of hazards. If the response is nonlinear, doesn't equation 3 lead to an erroneous factor in the final assessment?

B) The health effect classification scheme, and its basis for determination of the "severity factor" (Table 3)

- It is an excellent idea to classify different health responses based on the relative harmfulness of the effect. However, the factors used to calculate the SF would need more details so that different risk assessors would use the same factor for the same chemical.

Given the large proportion of subjective evaluation in determining the severity factor, combining hazard assessment and exposure assessment in one go might lead to bias caused by assessors subjective opinions. Small variation in x in ($0 < x < 1$ in the equation $SF = 10^{x}$) may cause large variation in final result

- Also it is worth noting that a chemical may have several types of health effects, and the SF should be calculated for all of them if there is quantitative data. The health effect with the lowest BMDL (which is usually used in determining the TDI or TWI levels) is not always the most severe. For example cadmium has been linked to estrogenic effects in some studies and it is considered a group I carcinogen, which are both more serious effects than the kidney enzyme marker level change. The RP / (AF x SF) may therefore vary for the same chemical depending on which endpoint is considered.

- If understood correctly, SAMOE is based on systemic effects. However, in Table 3 in page 23, local irritation or hyperplasia of epithelial or mucosal surface is an effect that leads to health effect classification. Even though local effects may also be important, the extent of their effect is based on concentration (mg/l) rather than on dose (mg/kg bw/day). Therefore, it is proposed that local effects are not taken into account in determining the hazard class.

- In table 3, it is mentioned that change of clinical chemistry parameter could lead to class 2a in hazard classification. However, in toxicological tests there

are almost always some deviations in clinical chemistry parameters. If there is no link to respective target organ toxicity, these effects are often disregarded. Therefore, hazard classification based only on clinical chemistry is not feasible.

C) The uncertainty model (section 4 in the report)

- To assess the uncertainty related to toxicity, significant variation in the metabolism of xenobiotics is found between humans of different genetical background. Mechanism of metabolism for the xenobiotic should be known so as not to underestimate the risk to the sensitive individual. This comment is not directed only to the Risk Thermometer but to the toxicity assessments worldwide.

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Ert Dnr: 1352/2014

Draft report: The Risk Thermometer – a tool for comparing risks associated with food consumption

Rapporten är ett välkommet bidrag till diskussionen om utveckling av riskbedömningsmetodik för kemikalier. Även om dess fokus är kontaminanter/tillsatser i föda är den användbar även för riskbedömning av kemikalier generellt. Den föreslagna metodiken bidrar till ökad transparens, t ex när det gäller val av bedömningsfaktorer och dess storlek, vilket vi tycker är positivt. Konceptet med större säkerhetsmarginal för ämnen som kan ge allvarliga effekter är intressant men kan eventuellt behöva utvecklas/modifieras (se nedan). Vi tycker också att det är positivt att det görs ett försöka att kvantifiera osäkerheten när det gäller riskbedömningen som helhet och att denna osäkerhet presenteras för beslutsfattare och allmänhet.

Nedan följer några mer specifika synpunkter på delar av rapporten:

Val av referenspunkt.

Vi tycker att det vore bättre om ett LOAEL-värde räknades om till ett beräknat NOAEL, t ex genom att det divideras med (åtminstone) en faktor 3 i enlighet med Reach-metodik, innan övriga beräkningar görs. Även om osäkerhetsanalysen beaktar att ett LOAEL-värde användes som utgångspunkt för riskbedömningen tycker vi att det blir lättare att följa riskbedömningen och tolka dess resultat om man gör som vi föreslår.

Severity factor (Tab. 3).

I stora drag tycker vi att förslaget verkar rimligt. När det gäller "Cancer" tycker vi dock att det vore lämpligt att skilja på genotoxiska carcinogener och de som sannolikt orsakar cancer via en tröskelmekanism. Vi noterar också att mutagenicitet saknas i tabellen. Det vore också bra om sensibilisering nämndes uttryckligt även om det kan inrymmas under "Immuntoxicitet 2b".

Eftersom de flesta toxiska effekter ökar i allvarlighetsgrad när exponeringen ökar kan många beräkningar behöva göras för att utröna vilken kombination av NOAEL/LOAEL, severity factor (SF) och AFs som ger lägst värde och därmed högst risk när man jämför med exponeringen.

Osäkerhetsanalysen

Det är positivt att osäkerheten i olika delar av riskbedömningen kvantifieras och redovisas (enligt Text box 2). Vi har inga synpunkter rörande förslaget om hur denna kvantifiering ska göras annat än att det är positivt att det framgår hur det har gjorts i varje enskilt fall.

Risk Thermometer examples

Även om det framgår av texten att exemplen som visas gäller för vuxna personer med medelintag via födan vore det värdefullt att komplettera dessa exempel med hur det ser ut för den aktuella riskgruppen för de fem olika exempelämnena (som alla är välkända och omskrivna problemämnen). Om det t ex rör sig om gravida kvinnor kan ju flera delar av riskbedömningen påverkas.

Salomon Sand UV_RN

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Ämne: Risk Thermometer Consultation - registration number 1352/2014

Please see the following comments from toxicology experts in the UK Food Standards Agency:

For genotoxic carcinogens, the approach is essentially what we currently do based on EFSA Scientific Committee guidance and WHO principles. Ranking is straightforward and informs risk management priorities.

The new approach relates to approaches for substances in food that are not genotoxic. Currently if we were asked to rank such substances we would say there is no concern if exposure is below a health-based guidance value. Risk could be ranked based on exceedance of the health-based guidance value if it occurs, and this is also understood by risk managers.

We consider that the report proposes a more conservative approach to non-genotoxic substances which we believe would lead to conclusions of concern about many authorised chemicals in food (food additives, pesticides, vet meds, food contact materials, etc). If that is the case, we consider that such conclusions would be subject to scientific and regulatory challenge, and not risk-proportionate.

The report notes that the approach is currently limited to chemical risks associated with chronic exposure. It mentions that it could be extended to cover acute effects of chemicals as well as risks associated with microbiological agents, but it was not clear how this might be achieved.

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Salomon Sand UV_RN

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Bifogade filer: The_Risk_Thermometer.pdf; Missiv_Draft_Risk_Thermometer.pdf

To Livsmedelsverket,

Nestlé is all aware of the deadline long passed for commenting on the enclosed documents sent to us by LI, and we apologize for the late answer.

The documents has been discussed internally at our Research Center among our Food Chemical Safety scientists and as they find this a very interesting report and approach, we have chosen to send you their comments and reflections even if the deadline has exired. They are:

- It may be a useful approach to evaluate, compare and prioritize compounds across different categories, including genotoxic carcinogens and mixtures using the margin of exposure. It sounds reasonable to start from the toxicity reference value, apply a severity factor depending on the hazard identified and compare it to the exposure.
- It would be interesting to see how it works for compounds with several sources of uncertainties coming both from the tox database and exposure. At least for the examples given it looks OK. The application of several uncertainty factors may make it over-conservative, but this maybe has to be shown in practice.
- One single SAMOE value does not tell you where the uncertainties and gaps are (compounds with poor database), and specialists would have to go back to the data used.
- For communication to consumers the thermometer may be a useful tool, but also other tools, perhaps like a traffic light system could be considered.
- The BfR approach is also mentioned, and it seems that the matrix the BfR use looks a bit different, more qualitative, and they don't come up with a single 'value'.
-

The severity classification scheme is indeed interesting: Such as the separation basically by irritation/corrosion, organ toxicity and carcinogenicity/developmental/repro tox.

With kind regards,

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LIVSMEDELSFÖRETAGEN
The Swedish Food Federation

Stockholm den 27 februari 2015

Till Livsmedelsverket
registrator@slv.se

Synpunkter på Livsmedelsverkets Risktermometer – reg nr 1352/2014.

Livsmedelsföretagen välkomnar möjligheten att få lämna synpunkter på Livsmedelsverkets rapport *"The Risk Thermometer – a tool for comparing risks associated with food consumption"*.

Då rapportens innehåll är på en hög detaljnivå och därmed svåråtkomligt för den som inte är sakkunnig i området hoppas vi att Livsmedelsverket påannonserat den öppna konsultationen för den grupp specialister som har kunskap att i detalj värdera rapporten.

Livsmedelsföretagen ser positivt på att verktyget Risktermometer tas fram som ett sätt att förbättra kommunikationen i frågor som gäller risker kopplade till livsmedel. Det kan ge möjlighet att nyansera de ofta snedvrida matlarmen som berör hela livsmedelssektorn inklusive företag och myndigheter. Vi hoppas på att få möjligheten att även kunna lämna synpunkter på del 4 – den grafik som ska visa resultatet av riskvärderingen. Det är av stor vikt att utformning och användning av denna grafik blir sådan att den inte vilseleder konsumenten. I all kommunikation där Livsmedelsverket använder Risktermometern, måste det vara tydligt vad verktyget är till för samt vad det inte är till för, t.ex. att den inte kan användas till att värdera risker med ensidig kost eller otillräcklig motion.

Livsmedelsföretagen vill vidare understryka vikten av att det föreslagna riskvärderingsverktyget är samstämmigt med den europeiska livsmedelsmyndighetens (EFSA) riskvärderingsarbete. Det är därför väsentlig att EFSA:s riskvärderingsmetod är utgångspunkten för Risktermometern. Risktermomentern får inte heller leda till att Sverige bedömer hälsoriskerna annorlunda (lindrigare/allvarligare) än EFSA.

Elisabet Rytter
Forskningsansvarig
Livsmedelsföretagen

LIVSMEDELSVERKET

Rapport 23 - 2014

The Risk Thermometer - a tool for comparing risks associated with food consumption

ALLMÄNNA SYNPUNKTER

Livsmedelsverkets rapport ger en bra översikt av de olika tillvägagångssätt vid riskvärdering av kemiska ämnen och produkter som tillämpas inom WHO/IPCS, EFSA, det tyska Federala Institutet för Riskvärdering (BfR) och USEPA. I rapporten understryks den viktiga tesen att *"Myndigheter behöver alltid prioritera användandet av resurser, för kemikalierelaterade frågor likväl som i andra avseenden."*

Även om riskerna med föroreningar från industrikemikalier i livsmedel i dagsläget oftast är minimal – vilket inte kan sägas om vissa naturligt förekommande toxiska ämnen - krävs att de ansvariga myndigheterna använder sig av en rationell och vetenskapligt välgrundad metodik för sin riskbedömning. Till skillnad från Kemikalieinspektionen, Naturvårdsverket och Folkhälsoinstitutet - vilka förutom Livsmedelsverket (SLV) ansvarar för utvärdering och kontroll av kemiska ämnen - har SLV i princip under lång tid grundat sina beslut på en *kvantitativ* riskvärdering, vilket minimerat vanligt förekommande godtyckliga och politiskt motiverade åtgärder. Den föreliggande ambitiösa rapporten ligger i linje med en tradition inom verket att upprätthålla god vetenskaplig praxis..

Med den rationella metodik som hittills används av SLV hade Folkhälsoinstitutet m.fl. organ inte kunnat prioritera dåligt underbyggda åtgärder mot bisfenol A och andra förmodade hot. Det anges att riktlinjerna är avsedda för *"myndighetens riskvärderingar för olika typer av ämnen som finns i maten"*. Även om detta ligger utanför SLVs ansvarsområde, medger rapportens generella utformning dock att samma tillvägagångsätt in princip kan användas vid en bedömning av luftföroreningar.

SLVs rapport är emellertid i stora delar svåråtkomlig för en inom riskvärderingens område mindre väl bevandrad läsare, och riktar sig till ett relativt begränsad grupp specialister som är dåligt, eller inte alls representerad i många av remissinstanserna.

Inledningen

Med tanke på den allmänna okunnighet som råder i det svenska samhället rörande riskvärdering av kemiska ämnen, hade det ur pedagogisk synpunkt varit värdefullt om WHOs definition av riskvärdering, samt innebörden i densamma, presenterats inledningsvis i sammanfattningen (framför allt i den svenska). Definitionen återges nu under "Risk assessment of chemicals" (sid. 10) och omfattar som bekant de fyra komponenterna

(a) faroidentifiering (kemikalieinspektionens språkbruk; "hazard identification") dvs. karakterisering av ämnets/produktens inneboende egenskaper,
(b) farokarakterisering (sambandet mellan dos och effekt; "hazard charcterization"),
(c) exponeringsanalys ("exposure assessment") samt

(d) kvantitativ riskbedömning ("quantitative risk assessment, risk characterization").

I rapporten presenteras olika risknivåer som kan tänkas föranleda riskbegränsande åtgärder, och det borde framhållas med skärpa, att denna *riskhantering,* till skillnad från riskbedömningen, *inte* är en vetenskaplig process utan grundar sig på administrativa/politiska överväganden. För en vanlig läsare av SLVs rapport, är denna är denna skiljelinje oklar.

Olika modeller för riskuppskattning

De olika tillvägagångssätten för riskuppskattning, och därmed sammanhängande begrepp, vilka organisationer som WHO/IPCS, EFSA, och USEPA använder, beskrivs tämligen utförligt i rapporten. I samtliga system utgör en på olika sätt vald *referensdos* eller kritisk exponering (RP, "reference point") utgångspunkten för riskbedömningen. Referensdosen – och därmed säkerhetsmarginalerna - modifieras genom användning av justerringsfaktorer ("adjustment factors" AFs) med utgångspunkt från vilka ingångsdata som använts (relevans, djurförsök/epidemiologiska data), målpopulation (vuxna, barn, variation i känslighet), m.m.. Referensdosen jämförs med en verklig eller beräknad exponering, vilket ger en säkerhetsmarginal (MOE, marginal of exposure) till vägledning för riskhantering. I likhet med tidigare praxis skiljer man mellan icke-genotoxiska och genotoxiska agentier. Medan i princip bedömningsmetodiken för icke-genotoxiska ämnen/blandningar icke nämnvärt skiljer sig mellan de ovan nämnda systemen, existerrar vissa skillnader vad avser den dos (BMD5, BMD10) som bedöms resultera i en 5% eller 10% ökning av en toxisk effekt i förhållande till bakgrunden ("benchmark response", BMR) genom att olika AFs tillämpas av de ovan nämnda institutionerna.

För carcinogena ämnen använder USEPA en mer vetenskaplig metodik (linjär extrapolering i lågdosområdet) som tillåter uppskattning av carcinogen potens ("slope factor") uttryckt som risk per mängd tillförd substans (mg/kg kroppsvikt och dag). Denna metodik resulterar i att riskbedömningen i USA kan skilja sig från den som genomförs av WHO/IPCS och inom EU. Oavsett vilket system som används är kan osäkerheten vid bestämning av referensdos avsevärd, särskilt om bedömningen grundats på djurförsök.

I den av SLV föreslagna komplexa metoden baserad på systemkoncept framförda av Burke et. al. (1996), Owen (2002), Krewitt et al., (2002) m.fl. införs en justering av referensdosen med avseende på skadans allvarlighet (SAMOE, "Severity-Adjusted Margin of Exposure") vilket oftast leder till ökade säkerhetsmarginaler. Vidare presenteras en modell för att uppskatta osäkerheten i SAMOE.

Allmänt om utvärdering av icke-genotoxiska och genotoxiska agentier

Senare forskning har på ett övertygande sätt visat att det i vissa fall inte existerar någon strikt skiljelinje mellan icke-genotoxiska och genotoxiska carcinogener (ger DNA-skador) vad avser dos-effekt samband. Även i frånvaro av extern exposition för carcinogena ämnen, uppstår ett stort antal DNA-skador i vår kropp som kontinuerligt och effektivt repareras (Swenberg et al., 2011). Till skillnad från DNA-molekylen i cellkärnan, existerar reparationsenzymerna för DNA i ett antal kopior. Exposition för substanser

som påverkar dessa enzymer, och därmed indirekt framkallar cancer, har därför oundvikligen en doströskel under vilken ingen ökning av cancerrisken kan förväntas. En riskbedömning av denna typ av substanser bör därför genomföras som för icke-genotoxiska ämnen.

Rapporten omnämner inte hur en riskbedömning av det stora antalet icke-genotoxiska carcinogena ämnen skall genomföras, t.ex. för livmedelstillsatsen butylerad hydroxyanisol BHA, peroxisomproliferatorer som läkemedlet nafenopin, m.fl.. Vissa alifatiska och cykloalifatiska kolväten utgör annan grupp icke genotoxiska ämnen, vilka hos råtta ger upphov till kroniska njurförändringar (nefros) som slutligen leder till adenom och carcinom i njuren (Bomhard et al., 1990).

Oorganisk arsenik (i-As) är ett genotoxiskt carcinogent ämne (inducerar kromosomaberrationer) som hämmar DNA-reparationen, och riskvärderingen bör därför utföras som för ett icke-genoxiskt ämne, vilket i själva verket sker. . (Nilsson et al., 1999; Hartwig et al., 2003; Andrew et al., 2006; . Ebert et al., 2011). Beroende på svårigheten att bestämma det intag av i-As i dricksvatten som framkallar cancer (företrädelsevis hud- och blåscancer), är osäkerheten stor vad avser den kritiska koncentrationen, men bör ligga i intervallet 200 - 300 µg/L. Den lägsta halten av i-As i dricksvatten som ger kromosomaberrationer (mikrokärnor) i perifera lymfocyter har bedömts ligga vid ca. 100 µg/L (Dulout et al., 1996).

SAMOE

Det av SLV föreslagna SAMOE-systemet är rationellt uppbyggt, men vid dess tillämpning finns en fara att riskvärderingen av kemiska ämnen reduceras till en matematisk exercis. Godtyckligt valda justeringsfaktorer med avseende på typ av toxisk effekt införs, och överväganden grundade på ämnesspecifika egenskaper ges en underordnad roll. Systemet ger orimligt stora säkerhetsmarginaler för vissa substanser, framför allt för carcinogener. Det framgår inte hur genotoxiska humancarcinogener skall bedömas. Den snarlika utvärderingsmodellen för riskbedömning och klassificering som publicerats av Owen (2002), och som SLV refererat till, avsåg endast icke-carcinogena substanser, vilket enligt vår uppfattning även borde gälla för klassificering enligt SAMOE.

Den föreslagna klassificeringsmodellen är svårbegriplig, och alltför komplex. För vissa ämnen som ger allvarliga toxiska effekter är det inte alltid befogat att införa en extra säkerhetsfaktor på 100, t.ex. där dos-responskurvan är brant, och tillåter att med relativt god precision fastställa en NOAEL. Eftersom referensdosen (RP) redan justerats nedåt för genotoxiska carcinogener i den metodik som t.ex. EFSA och USEPA använder, innebär att en ytterligare, omotiverad säkerhetsfaktor på 100 (för skadans allvarlighetsgrad), att SAMOE inte kan tillämpas på oorganisk arsenik (i-As) och många andra carcinogener.

USEPAs insatser för riskvärdering av cancerframkallande kemikalier måste anses ha varit banbrytande. Vid sina utvärderingar ger denna myndighet avsevärt utrymme för den modifierande rollen som *verkningsmekanismen* ("mode of action") kan ha. För icke-carcinogena ämnen anges visserligen 'på sid. 12 i SVL-rapporten en rad faktorer (AFs) - som datakvalitet, relevans för populationen, m.fl. - vilka kan påverka fasställandet av referensdosen (RP), men i rapporten framgår inte hur denna aspekt skall tillvaratas för carcinogena

ämnen. Detta är en brist, eftersom dylika faktorer påverkar bl.a. det föreslagna, men dåligt beskrivna klassificeringssystemet, där det är oklart om klassificeringarna på sid. 23 avser data från djurförsök såväl som humandata.

Under "Toxicitet med avseende mag-tarmkanalen" (sid. 23) inkluderas "irritation, hyperplasi" i klass 2 (intermediär nivå vad avser skadans allvarlighet), medan carcinogener placeras i klass 3 (högsta nivå vad avser skadans allvarlighet). Livsmedelstillsatserna BHA (IARC, 1986) och propionsyra (Harrison, 1992) ger upphov till såväl hyperplasi som tumörer i förmagen på råtta, och skulle således i detta system inkluderas i klasserna 2 och 3, vilket inte är rimligt. BHA och propionsyra borde rimligtvis hamna i den lägsta faroklassen.

Tillämpning av SAMOE på toxiska ämnen i mat och dryck – några exempel

I SLV-rapporten ges fem exempel på ämnen utvärderade enlig SAMO;: *Bly, polyklorerade dioxiner och PCB, kadmium och bisfenol A* har utvärderats som icke-carcinogener. *Hexaklorbensen* ger tumörer hos gnagare vid höga doser, men bör i strid mot SLVs uppfattning, betraktas som icke-genotoxiskt (EPA-IRIS). Valet av justeringsfaktorer baserad på typ av toxicitet, samt osäkerhetsmarginaler presenteras ingående. I samtliga fall uppges SAMOE ge drastiskt lägre säkerhetsmarginaler än de MOE som rekommenderas t.ex. av EFSA. SAMOE ger en faktor 3 i stället för 7 för bly, 2 i stället för 52 för polyklorerade dioxiner och PCB, 2 i stället för 7 för kadmium, 380 i stället för 3100 för bisfenol A och 1700 i stället för 840 000 för hexaklorbensen.

I djurförsök har för hexaklorbensen en NOAEL (en dos som inte framkallar skadlig påverkan) med avseende på leverskador på mellan 0.05 och 0.07 mg/kg kroppsvikt och dag fastställts. International Program on Chemical Safety (IPCS) har rekommenderat en säkerhetsdos ("health based guidance value") på 0,17 µg/kg/dag. Substansen har bedömts vara icke-genotoxisk (EPA-IRIS), men framkallar tumörer i djurförsök. På basis av induktion av levertumörer hos råtta har EFSA angivit ett BMD5 på 170 ng/kg kroppsvikt och dag,

Det rapporterade dagsintaget i Nederländerna 1996 var 1,4-3,1 ng/kg/dag, 5 ng/kg/dag i Sverige (1975-1990), medan lägre intag uppmätts i USA. Enligt EFSA ligger säkerhetsmarginalen (MOE) på mellan 160 000 och 8 000 000 (EFSA, 2006). Att en icke-genotoxisk carcinogen som hexaklorbensen (EPA-IRIS), där relevansen för tumörindiktion dessutom kan ifrågasättas på mekanistiska grunder (EFSA, 2006), belastas med en ca. 500 gånger lägre säkerhetsmarginal i förhållande till en konventionell utvärdering kan inte accepteras.

För nedan presenterade toxiska ämnen ger även den av EFSA tillämpade metodiken så höga säkerhetsmarginaler (MOE) att de är vanskliga att tillämpa i form av administrativa åtgärder. Med SAMOE ter sig resultaten i än högre grad verklighetsfrämmande.

Oorgansk arsenik - EFSA (2014) har uppskattat det genomsnittliga intaget för i-As inom EU till mellan 0,09 och 0,38 µg/kg/dag (95% percentil, 0.14 - 0.64 µg/kg) dvs 5 till 23 µg (95% percentil, 8-38 µg/kg) för en person som väger 60 kg. EFSA fastställde en BMDL10 (det nedre konfidensintervallet för

en dos som motsvarar en 10% ökning i förhållande till bakgrunden) på mellan 0,3 och 8 µg/kg/dag for en ökad cancerrisk och risk och för hudlesioner (EFSA CONTAM Panel, 2009), vilket motsvarar ett dagsintag på 18–480 µg för en person som väger 60 kg. Den nedre delen av dosområdet motsvarar normalintaget hos en stor del av Europas befolkning, vilket innebär att det lägre intervallet för BMDL10 inte är rimligt.

För Japaner med en avsevärd konsumtion av marina alger (hijiki) med betydande halter i-As (400-2800 µg/kg) är dagsintagen än högre (Rose et al., 2007; Nakamura et al., 2008). Den Japanska populationen kännetecknas av en mycket låg incidens hudcancer, där de förändringar som är typiska för kronisk exposition för i-As (bl.a. annan lokalisering än för UV-inducerade lesioner) inte kan undgås att upptäckas. Även om en justerringsfaktor (AF) för referensdosen (RP) sätts lika med 1, kommer SAMOE-systemet ge en gigantisk övervärdering av risk för i-As, och skulle medföra förbud, inte bara mot försäljning av hijiki, men även för marina skaldjur som hummer och räkor.

I SLV-rapporten refereras till godtagbara säkerhetsmarginaler (MOE) uppgående till 10 000 för gentoxiska ämnen som visats vara carcinogena i djurförsök. För humancarcinogener där det finns en någorlunda tillförlitlig information, är en dylik säkerhetsfaktor givetvis orealistisk stor. Den av WHO rekommenderade konservativa standarden för i-As i dricksvatten från 1993 baserad på humandata, och som gäller inom EU (1998), ligger på 10 µg/L (reducerad från 50ug/L), och avspeglar således en säkerhetsfaktor på 10-30 som är jämförbar med vad som tillämpas på icke carcinogen substanser.

Etylkarbamat (uretan) är ett genoxisk carcinogen som förekommer i alkoholhaltiga drycker, bröd, sojasås och yoghurt. På grundval av djurförsök erhöll EFSA ett BMD10 på 0,3 mg/kg/dag. Mediankoncentrationerna i öl har befunnits ligga vid 5 µg/kg, i vin 10-11 µg/kg och i starkvin 32 µg/kg. Högsta medianhalterna har påträffats i sake (122 µg/kg), cognac (123-129 µg/kg), vodka och rom (325-387 µg/kg) samt för spritsorter från frukt som plommon (šlivovica), aprikoser (barack pálinka, Marillenschnaps, m.fl.) och äpplen (calvados), där medianhalterna befanns ligga mellan .663 och 851 µg/kg. Vissa spritsorter från stenfrukt kan uppenbarligen innehålla över 20 000 µg/kg av denna carcinogena substans.

Säkerhetsmarginalen (MOE) för normalkonsumenter av olika födoämnen samt visst intag av alkoholhaltiga drycker uppskattades till ca. 5 000. SAMOE skulle reducera denna säkerhetsmarginal med en faktor 100 till det orimligt låga värdet 50, och om hänsyn dessutom tas till det faktum att etanol omvandlas till carcinogent acetaldehyd, skulle det knappast finnas någon acceptabel säkerhetsmarginal. För konsumenter av spritsorter från stenfrukt är enligt EFSA MOE mindre än 600 (EFSA, 2007). En tillämpning av den överdrivna, och orealistiska riskbedömning som genereras av SAMOE, skulle med säkerhet medföra att Systembolaget fick rensa ut stora delar av sitt sortiment.

α-Solanin och and α-chaconin är två för människa neurotoxiska glykoalkaloider som förekommer i potatisväxter. I försöksdjur induceras även embryotoxiska och teratogena skador. Data föreligger från subakuta undersökningar, men märkligt nog har inga kroniska studier kunnat påträffas i

litteraturen.

Växtförhållanden har stor betydelse, men halterna i hela potatisknölar ligger vid 43-97 mg/kg, medan koncentrationen i köttet har uppmäts till mellan 12 och 50 mg/kg. En toxisk dos för människa på 2-5 mg/kg har angivits (ILS, 1998).

SLV påpekar att säkerhetsmarginalen mellan de halter av glykoalkaloider som finns i normal potatis, och de halter där människor skulle kunna få en lindrig förgiftning är liten, uppskattningsvis en faktor 2-6 (SLV, 2014).

Glycyrrhizinsyra är en kortisolanalog med hormonstörande egenskaper som förekommer i lakrits. Substansen hämmar 11-beta-hydroxysteroid dehydrogenas, som omvandlar kortisol till kortison. Vid en kontinuerlig exposition kommer nivån av kortisol att hållas hög, vilket påverkar hormoner som reglerar saltbalansen (renin-angiotensin-aldosteron). Detta kan i sin tur leda till hypertension, ödem, hjärtproblem och flera andra typer av besvär.

Halten glycyrrhizinsyra ligger inom intervallet 0,29-7,9 mg/g konfekt, och i det stora flertalet fall under 3,5 mg/g. Vissa "hälsokostprodukter" med lakrits innehåller betydligt högre halter glycyrrhizinsyra (15-47mg/g), och i ett fall rapporterades en lakritsprodukt ha 0,3 procent glycyrrhizinsyra. Ett dagsintag av ca 100 mg glycyrrhizinsyra (motsvarar 50 g lakritskonfekt), synes vara en lägsta dos vid vilken toxiska effekter uppträder (Andersson et al., 1995). I likhet med glykoalkaloiderna i potatis är säkerhetsmarginalen mycket låg.

Man kan givetvis invända, att vi har lång erfarenhet av såväl potatis som lakrits, men kan inte undanskymma det faktum, att grundat på solida vetenskapliga principer, ett normalintag av vissa av våra vanliga livsmedel medför risknivåer som är helt oförenliga med ett system som SAMOE, och i vissa fall även med det EFSA tillämpar.

Tobaksspecifika nitrosaminer (TSNA) - Ett högt intag från tobak av de tobaksspecifika nitrosaminerna NNK (4-(nitrosometylamino)-1-(3-pyridyl)-1-butanon) och NNN (N'-nitrosonornikotin) inducerar tumörer i såväl försöksdjur som människa (Winn et al., 1981; Idris et al., 1991, 1994; Ahmed and Mahgoob, 2007; IARC, 2007). Hos människa framkallar en rökfri tobak, som är starkt förorenad med TSNA, framför allt tumörer i munhåla och svalg, men det har däremot inte varit möjligt att med internationellt accepterade standardmetoder inducera tumörer i djurförsök med snus som sådant från USA eller Sverige.

Dagens svenska snus uppvisar halter som är 2 000 (NNN) till 10 000 (NNK) gånger lägre än för cancerframkallande Sudanesisk snus (SLV, 2002; Idris et al., 1991). De första mätningarna av TSNA i svenskt snus genomfördes av SLV 1983, och gav en genomsnittlig NNK-halt på 3,2 µg/g och 7,6 µg/g för NNN (avser torrvikt). Detta motsvarar ett dagsintag från 20g snus (50% vatten; 60% absorption) på 0,27 µg/kg/dag från NNK och 0,65 µg/kg/dag från NNN. Även mot bakgrunden av dessa data, har det inte varit möjligt att påvisa, vare sig en förhöjd cancerrisk eller andra allvarliga toxiska effekter vid användning av svenskt snus (Lewin et al., 1998; Schildt et al., 1998; Lee 2011). Dagens svenska snus innehåller halter som är lägre än en 10-del av de som uppmättes 1983; 0,2 µg/g för NNK och 0,5 µg/g för NNN (SLV, 2002).

På grundval av två mindre studier har det hävdats att det föreligger ett verifierat orsakssamband mellan skandinaviskt snus och pankreascancer

(Boffetta et al., 2005; Luo et al., 2007). Denna slutsatsa är felaktig. I dessa studier hade bl.a. hänsyn inte tagits till de viktiga konkurerande orsaksfaktorerna alkoholmissbruk och diabetes. Sammanställningen av data från ett stort antal undersökningar utförd inom ramen för "*the International Pancreatic Cancer Case–Control Consortium*" med Boffetta som "senior author", där hänsyn tagits till alkohol och diabetes, och som omfattande 6056 fall och 11,338 kontroller, utvisade att det inte förelåg någon förhöjd risk i pankreascancer till följd av konsumtion av rökfri tobak (Bertuccio et al., 2011).

Säkerhetsmarginalen för uppkomst av cancer vad avser exponering för NNK och NNN i modernt svenskt snus baseras nedan på information från epidemiologiska studier, djurförsök och molekylärbiologiska data.

Epidemiologiska data har den nackdelen att vi saknar tillförlitliga uppgifter i dosintervallet för intag på 0,92 µg/kg/dag för NNK plus NNN (svenskt snus 1983) upp till de koncentrationer som påträffas i sudanesiskt snus (Nilsson, 2011), dvs. 96–938 µg/kg/dag för NNK plus NNN. För metadata från svenska epidemiologiska studier fann Lee (2011) en relativ risk (RR) uppgående till 1.01 (95% CI 0.71-1.45). Incidensen tumörer i nasopharynx ligger i Sverige vid ca. 10 per 100 000 (NORDCAN, 2012), varvid minst ca. 8 fall kan tillskrivas rökning. Den statistiska upplösningen i de svenska snusstudierna har varit tillräcklig för att upptäcka en 50% ökning av bakrundsincidensen. Detta innebär att resultaten teoretiskt medger existensen av ca.1 fall per 100 000 snusare, vilket måste anses som en godtagbar risk. Användningen av data från djurförsök antyder att den verkliga risken förmodligen är ännu lägre.

Djurförsök – Vid kronisk oral tillförsel framkallar NNK tumörer näshåla, lever, lunga och pankreas. För lunga är dos-responskurvan över 20 µg/kg/dag approximativt linjär (Rivenson et al., 1988), med en BMD10 på ca. 25 µg/kg/dag. Dagens svenska snus ger ett dagsintag för NNK den mest potenta carcinogenen, på 0,017 µg/kg/dag vilket ger en MOE på ca. 1 500, vilket torde representera en tillfredsställande säkerhetsmarginal. För den mindre potenta NNN erhålles en högre MOE. Men med en justering med ytterligare en faktor 100 av den kritiska dosen erhålles en orealistisk SAMOE för NNK i snus på 15.

Med tanke på att de svenska epidemiologiska studierna reflekterar ett intag av snus som sträcker sig över flera decennier, stämmer dessa resultat väl överens med en LOAEL baserad på epidemiologiska data. Ovanstående beräkningar är inte korrigerade för speciesskillnader, men molekylärbiologiska data antyder att det inte förekommer signifikanta differenser mellan råtta och människa vad avser metabolisk aktivering av TSNA (se nedan).

Riskvärdering av carcinogener grundad på molekylärepidemiologiska data, en bortglömd aspekt

Genom molekylärbiologiska analyser kan pro-carcinogena effekter påvisas långt under de som kan bestämmas vid konventionella epidemiologiske studier. Det är allmänt accepterat, att en DNA-skada som inte repareras - eller reparers felaktigt - är en första - men icke tillräcklig förutsättning för uppkomsten av en cancertumör. Även hos "icke exponerade" individer uppkommer kontinuerligt en mängd DNA-skador, vars ursprung är oklar, men där tarmfloran och dieten spelar en viktig roll (Swenberg et al., 2011). Dosen i DNA i den kritiska vävnaden representerar den egentliga måldosen, och dess bestämning onödiggör andra dosbegrepp. Pro-mutagena (pro-carcinogena) DNA-skador

kan anses vara surrogatindikatorer för cancerrisk, men en exponering för en carcinogen substans som leder till nivåer för ämnet specifika DNA-skador som ligger signifikant *under* den naturliga bakgrundsnivån, måste anses representera en exposition som inte medför någon cancerrisk (NOAEL, "no-observed-adverse effect level").

Formaldehyd är ett genotoxisk carcinogen (IARC, 2006) som ger upphov till DNA skador (addukter) av typ N^2-hydroxymetyldeoxyguanosin. Incidensen carcinom i nässlemhinnan hos råtta efter inhalation av formaldehyd uppvisar en kraftig, icke linjär ökning först vid halter överstigande 2 ppm. Genom att formaldehyd utgör en normal produkt vid den cellulära metabolismen, påträffas signifikanta nivåer av dessa DNA addukter normalt i människans olika vävnader samt hos icke exponerade försöksdjur. Genom att ta hänsyn till den "naturliga" bakgrunden av dessa DNA-addukter, samt basera riskuppskattningen på molekylärbiologiska data, erhålles riskestimat som är signifikant lägre än vad USEPAs beräkningar utvisat på basis av humandata och konventionell metodik (Swenberg et al., 2011).

Tobaksspecifika nitrosaminer. Metabolisk aktivering av NNK leder till reaktiva intermediärer som ger olika s.k. DNA-addukter (Hecht, 1999), framför allt 7-metylguanin (7-mGua), O6-metylguanin (O6-mGua) och olika pyridyloxy-butyladdukter (POB). NNN ger endast POB-addukter. O6-mGua är en starkt pro-mutagen och pro-carcinogen DNA-skada, vilket i mindre utsträckning gäller POB-addukterna. 7-mGua anses ha en låg pro-mutagen och pro-carcinogen profil. TSNA genererar även POB-addukter i hemoglobin. Kinetiken för bildningen av dessa addukter har studerats i detalj i försöksdjur och en sammanfattning av resultaten har publicerats av Nilsson (2006, 2011).

Av betydelse i detta sammanhang är det faktum att DNA i vävnader från icke exponerade individer normalt innehåller samma addukter i koncentrationer på mellan 1 addukt per 10^7-10^9 normala nukleotider (TN). Endast ett fåtal laboratorier har de avancerade och känsliga specialmetoder som krävs för dessa analyser (numer inte något laboratorium i Sverige). Metyladdukterna förekommer i de högsta koncentrationerna, och kan förutom från TSNA bildas från andra exogena och endogena källor. POB-addukter har tidigare ansetts som specifika för TSNA, men förekommer – till skillnad från hos försöksdjur - även i signifikanta nivåer i individer som aldrig exponerats för TSNA i tobak. Det har föreslagits att alkaloiden myosmin, som förutom i tobak förekommer i signifikanta koncentrationer i ett antal livsmedel, utgör källan till PBO-DNA-addukter hos icke exponerade individer (Zwickenpflug, 2000; Wilp et al., 2002; Zwickenpflug et al., 2005).

Bl.a. på grund av att icke exponerade gnagare inte innehåller någon detekterbar bakgrund av metyl- och POB-addukter, är den metodik som används av EFSA (samt i SAMOE) för att fastställa en kritisk exponering (RP) på basis av en BMD10 eller PARP inte tillämplig. I stället kan en realistisk säkerhetsmarginal baseras på jämförelsen mellan de "normal" addukthalter som uppmätts hos människa och de koncentrationer baserade på djurförsök och som kan förväntas från intag av 20g svenskt snus.

Med ledning av värdena i Tabell 1 erhålles en säkerhetsmarginal i förhållande till bakgrunden på mellan 900 och 14 000 för den mest pro-carcinogena addukten O6-mGua i lunga, och motsvarande värden för lever ligger på mellan 9 000 och 60 000. Den mycket lägre

förväntade adduktnivåerna i lever beror på effektiv DNA-reparation i detta organ. De stora variationerna i analysdata beror på individrelaterade skillnader samt de tekniska svårigheterna att bestämma dessa låga nivåer av O6-mGua. För 7-mGua och POB-addukter, vilka förekommer i högre koncentrationer, ligger nivåerna på mellan 700 och 1900 *under* bakgrunden.

Tabell 1. Jämförelser mellan DNA-addukthalter hos råtta jämfört med halterna uppmätta i motsvarande vävnader hos människa. Förväntade adduktkoncentratiner erhölls genom att multiplicera intaget av resp. TSNA med effektiviteten för alkylering i råttvävnad (från Nilsson, 2011)

Typ av DNA-addukt	**Addukthalter uppmätta hos människa (addukter per 10^9TN)**	**Förväntade addukthalter baserade på data från råtta (addukter per 10^9 TN)**	
O6-mGua Lunga Lever	25–380 28–168	53–674 5–67	0.027 0.003
7-mGua *Lunga,* icke rökare	250 650	689–8672	0.35
POB–DNA addukter (totalt) Lunga, icke rökare	24-28	25–240	0.03
		Sudanesiskt snus; Intag (µg/kg/dag) NNK = 53–674 NNN = 43–264	Svenskt snus; Intag (µg/kg/dag) NNK = 0,017 NNN = 0,042

TN= totala antalet normala nukleotider (TN)

Eftersom den "normala" bakgrundsnivån för pro-carcinogena DNA-addukter hos människa utgör referenspunkten, är det uppenbart att konsumtion av snus från Sudan kan förväntas innebära en signifikant cancerrisk. Under antagandet att den genomsnittliga "normala" bakgrundsnivån för O6-mGua i lunga hos människa är 200 addukter per 10^9 normala nukleotider, utgör 20 addukter en 10% ökning av bakgrunden. Dos-responskurvan för dessa DNA-addukter är linjär inom ett stort intervall skenbart ned till origo. 20 Addukter motsvarar ett intag av NNK på ca. 20 ug/kg/dag, vilket ger en säkerhetsmarginal (MOE) på ca. 1200. Baserat på det lägsta uppmätta bakgrundsvärdet för lever på 28 addukter per 10^9 nukleotider, erhålles en säkerhetsmarginal (MOE) på ca. 9000. Beroende på de varierande uppgifter som förekommer i litteraturen angående DNA-skador hos "icke exponerade" individer, är de nyss nämnda uppskattningar osäkra. Likväl avviker de icke avsevärt från utvärderingarna genomförda med konventionell metodik.

En berättigad invändning är om dessa data från försöksdjur kan extrapoleras till människa. När det gäller NNK och NNN finns det

goda belägg för att detta låter sig göras. Som omnämnts ovan, leder metabolisk aktivering av dessa nitrosaminer till att samma aktiva intermediärer alkylerar såväl DNA som hemoglobin. För POB-hemoglobin (Hb) finns data tillgängliga för snusare, och Hb-addukterna kan användas som surrogat-indikatorer för aktivering av TSNA. Den *ökning* av nivån dylika addukter som uppmätts hos snusare i förhållande till kontroller överensstämmer väl med vad som förväntas på grundval av djurförsök (Nilsson, 2011).

Sammanfattning - Ovan presenterade beräkningar indikerar säkerhetsmarginaler för befarad uppkomst av cancer från intag av dagens svenska snus på över 1200. Dessa värden är jämförbara med motsvarande värden för flera andra föroreningar i livsmedel, och är betydligt mer betryggande än vad som gäller t.ex. för etylkarbamat och etanol/acetaldehyd i spritdrycker, lakrits och oorganisk arsenik.

SAMMANFATTANDE KOMMENTARER

Den av SLV föreslagna komplexa SAMOE-metodiken är logiskt uppbyggd och ligger i linje med en god tradition att grunda administrativa beslut på en *kvantitativ* riskvärdering, vilket skulle kunna minimera diverse godtyckliga och politiskt motiverade åtgärder i Sverige.

SAMOE är dock i alltför hög grad en skrivbordsprodukt , där det finns en fara att riskvärderingen av kemiska ämnen reduceras till en matematisk exercis, vilken för många enskilda agentier aldrig kan ersätta expertbedömning. Det framhålles att "Syftet är att underlätta för konsumenter och media att förstå och förhålla sig till risker med olika ämnen". I sin nuvarande svårgenomträngliga utformning, torde detta mål inte kunna uppnås.

Det är i och för sig rimligt, att vid en riskbedömning ta hänsyn till allvarlighetsgraden för befarade skador. Men SAMOE inför godtyckligt valda justeringsfaktorer i detta avseende, och överväganden grundade på ämnesspecifika egenskaper riskerar att få en underordnad roll. Systemet ger orimligt stora säkerhetsmarginaler för i livsmedel vanligt förekommande toxiska substanser, framför allt för carcinogener. Eftersom referensdosen, som utgör utgångspunkten för bestämning av säkerhetsmarginaler, redan justerats nedåt för genotoxiska carcinogener i den metodik som t.ex. EFSA och USEPA använder, innebär att en ytterligare säkerhetsfaktor på 100 är omotiverad. För icke-genotoxiska substanser med t.ex. hormonstörande påverkan, kan SAMOE leda till rätt bisarra konsekvenser, exempelvis för det ovan beskrivna exemplet med lakrits, men även för fytoestrogenerna coumestrol, genistein, och daidzein, av vilka åtminstone coumestrol (i sojaprodukter, m.m..) är betydligt mer potent än bisfenol-A.

En allmän tillämpning av SAMOE riskerar att få negativa konsekvenser för livsmedelsproduktion och handel, vilket i sin förlängning t.o.m. kan leda till "non-tariff barriers of trade". Det finns få skäl att frångå den metodik för riskbedömning som tillämpas av the European Food and Safety Authority (EFSA). Förvisso kan EFSAs metodik förfinas, men det rätta tillvägagångssättet vore härvidlag att detta genomförs i samråd med denna institution. Det vore

mycket olyckligt om ett parallellt system införs i Sverige.

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Draft report

The Risk Thermometer – a tool for comparing risks associated with food consumption

Livsmedelsverket Rapport 23 – 2014

Svensk Dagligvaruhandel har beretts tillfälle att yttra sig över rapporten.

Bakgrund

Syftet med rapporten är att ge Livsmedelsverket bättre metoder för att kunna göra riskbaserade prioriteringar av verksamheten t ex genom att förbättra kontrollverksamheten. Verktyget, kallat Risktermometern, är utvecklat för att förtydliga och göra det lättare att jämföra slutsatserna av myndigheternas riskvärderingar för olika ämnen som finns i maten. Det kan användas för miljögifter, metaller, bekämpningsmedel och tillsatser.

Livsmedelsverket skriver: "Verktyget kan, exempelvis konsumenter och media, använda för att förstå och förhålla sig till risker med olika ämnen. Tanken är att det i framtiden ska bli enklare att kommunicera hur stor risken bedöms vara med olika ämnen i maten."

Svensk Dagligvaruhandel har följande att anföra.

Svensk Dagligvaruhandels medlemmar har stor erfarenhet att arbeta med allehanda risker under många år. Svensk Dagligvaruhandel är mycket skeptiska till att det är möjligt att göra denna typ av riskvärderingar. Risken är stor att det blir sådana förenklingar att det blir direkt missvisande. I verktyget saknas bl a arbetsmiljö aspekter.

Med hänsyn till att kemikalier och risker är svåra att förstå, och vanligtvis mycket laddade, vill vi varna för en användning som riktar sig till konsument och media.

Svensk Dagligvaruhandel ställer sig inte bakom detta sätt att kommunicera risker på. Vi är gärna med och diskuterar frågan, men kan inte med nuvarande information se att detta skulle gynna varken branschen eller konsumenterna.

Stockholm 2015.03.09

Svensk Dagligvaruhandel

Per Baummann