Risiken erkennen – Gesundheit schützen

Harmonised approach for the risk assessment of compounds which are both genotoxic and carcinogenic

Opinion No. 028/2005 of 18 May 2005 on EFSA's Draft Opinion of 7 April 2005

The European Food Safety Authority has prepared a draft for a harmonised strategy for the risk assessment of genotoxic and carcinogenic substances and presented this draft for discussion. The concept examines the exposure of the consumer to a specific substance and compares this with the carcinogenic effect of a defined dose in an animal experiment. Genotoxic and carcinogenic compounds are thus to be classified according to their potential risk.

The Federal Institute for Risk Assessment has voiced its opinion on the EFSA draft. In principle, the Institute welcomes the concept. However, BfR recommends - amongst other things - that this strategy be pursued in addition to the previously used ALARA (as low as reasonably achievable) principle and not instead of it. If the new strategy is used in isolation, the Institute believes there is a risk that the application of the minimisation principle to **all** genotoxic and carcinogenic substances without exception, the current practice, will be undermined. The Institute has explained the reasons for its opinion to the Federal Ministry of Consumer Protection, Food and Agriculture. This document can also be accessed on our homepage (http://www.bfr.bund.de/cm/245/risk_assessment_of_genotoxic_and_carcinogenic_substances_to_be_harmonised_in_the_eu.pdf (in English) or http://www.bfr.bund.de/cm/208/risikobewertung_genotoxischer_und_kanzerogener_stoffe_soll_in_der_eu_harmonisiert_werden.pdf (in German)) .

General comments

The Federal Institute for Risk Assessment welcomes the draft opinion presented as an approach to assessing the risk of genotoxic and carcinogenic substances. Thus risk managers have been given a basis for setting priorities for taking action to minimise the risk for consumers.

BfR is of the opinion that the Margin of Exposure (MOE) approach presented by EFSA's Scientific Committee (SC) could be an acceptable approach to comparing the risks of genotoxic and carcinogenic substances. Recently, the Joint FAO/WHO Expert Committee on Food Additives calculated MOEs for substances that are both carcinogenic and genotoxic and considered the calculated MOE for acrylamide to be too low (ftp://ftp.fao.org/es/esn/jecfa/jecfa64_summary.pdf).

The Institute prefers the benchmark approach to calculating the point of comparison (if data are available) to the T25 approach also mentioned. The benchmark approach uses dose levels (from animal experiments or human exposure) that are in general quite well known whereas calculation of the point of comparison with the T25 method does not include the dose-response relationship. Therefore, and with a view to risk communication of the proposed risk assessment strategy, the benchmark approach seems to be more appropriate than the risk extrapolation via the T25 method, which is a more speculative method although the T25 method is used widely within the risk assessment of chemicals (http://ecb.jrc.it/REACH/) and by the Scientific Committee on Consumer Products SCCP as published in its Notes of Guidance (http://europa.eu.int/comm/health/ph_risk/committees/sccp/documents/out242_en.pdf).

BfR notes that for the first time a risk assessment approach is recommended using the Margin of Exposure (MOE) whilst, at the same time, giving guidance by setting a certain risk level for existing risks that are present in our environment and food. The SC offers the view that a MOE of 10,.000 or higher would havebe o af low health risk. However, BfR underlines the statement by the SC that the acceptability of a MOE is a societal judgement and should be discussed under the responsibility of risk managers.

BfR cannot take a position on the societal acceptability of a MOE of 10,000, but can only make a judgement on the scientific basis of the factors discussed for calculating an overall MOE. The Institute considers that these factors are reasonable and scientifically well based.

6. BfR is of the opinion that priority setting cannot be based on a simple calculation of the MOE. It is the responsibility of risk assessors to take all known and lacking data into consideration for their case-by-case assessment. Moreover, it is not clear whether possible combination effects of various genotoxic and carcinogenic substances present in food were discussed within the SC. BfR emphasizes that exposure towards structurally related substances for each of which a MOE is assessed could lead to a lower overall MOE for the group of substances in question (e.g. exposure to structurally related substances like methyl eugenol, estragole and safrole or nitrosamines).

Although the calculation of a MOE offers risk managers the possibility of setting priorities for taking action to minimise the risk for consumers, the ALARA principle for all genotoxic and carcinogenic substances should not be questioned at all. Especially, the MOE is only as accurate as an estimation of human dietary exposure can be and can differ from the exposure scenarios chosen. Moreover, the estimation of human dietary exposure is crucially dependent on the choice of dietary intake studies.

BfR questions if the SC took into account the fact that carcinogenic substances exist where genotoxic properties only contribute to a minor extent to their carcinogenicity.

The Institute recommends discussing more intensively the uncertainties of a MOE when calculated on the basis of different quality of data.

Summary

In general, the proposed harmonised approach for risk assessment of compounds which are both genotoxic and carcinogenic can be accepted. The approach offers a sound basis for the risk assessment if a comparison of risks is needed. However, the argumentation should meet known standards, especially for setting default values, as published by the WHO/ILO/UNEP International Programme on Chemical Safety (“Guidance values for health-based exposure limits: Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits (EHC No 1701994)”, http://www.inchem.org/documents/ehc/ehc/ehc170.htm, and “- Human health risks - Principles for the assessment of risks to human health from exposure to chemicals (EHC No. 210 (1999)“ http://www.inchem.org/documents/ehc/ehc/ehc210.htm).

There should be a discussion on specific points as pointed out in the comments hereafter.

Specific comments

The calculation of a MOE does not offer the possibility of quantifying risks. Specifically, the MOE is an “uncertainty (safety) factor”. Therefore, it should be stated more clearly that the

MOE approach does not allow the calculation of risks. It is further proposed to describe the MOE approach as the preferable approach in comparison with the unit risk approach, which is not related to real life exposure.

BfR supports the proposal to take “consumers only” instead of the whole population for intake estimates.

The Institute also supports the general opinion that different nutrition studies could deliver data for the assessment of chronic risks. But the different study protocols (e.g. 7 days weighing protocol, 24-h-recall, diet history method) could show different intakes accounting for different exposure scenarios in calculating the MOE and therefore influence risk assessment.

Moreover, categories of food are covered differently by the protocols. A quite good picture of highly consumed food is often gained. However, rarely consumed foods are covered differently by various methods. It could be that such food is not covered at all in a given study. Therefore, the SC approach should point out these differences.

The scientific reasoning behindof uncertainty factors should be described more thoroughly. It should be explained more clearly why those factors are used and how they are derived.

a) For factor 100 in Item 3.1 ‘Consideration of inter- and intraspecies differences’ line 473 it is said that "these 10-fold factors allow for physiological and metabolic differences and these would also be relevant....". It should read as:’- toxicokinetic (mainly differences in rate of metabolism) and toxicodynamic (mainly intensity of response) differences’.
b) The explanation given in lines 477 to 487 are true for the contribution of toxicokinetics (interspecies factor of 4 and intraspecies factor of 3.2 (WHO/ILO/UNEP International Programme on Chemical Safety)) to the factor 10 but not for the toxicodynamics part. The aspect of possible toxicodynamic variability is drawn correctly under Item 3.2 ‘Additional considerations relating to the carcinogenic process’. The right consequences are drawn to take into consideration very high variability, e.g. because of polymorphism. Therefore it seems to be even better to delete lines 488 to 492 and to explain in line 546 ‘..... referred to above, that the combined factor for inter- and intraspecies variability should be greater than the usual default value of 100 taking into consideration the wide variability which is due to polymorphic expression of genes relevant for cancer susceptibility, in particular for DNA repair and cell cycle control. Thus, the Scientific Committee considers it appropriate to add another factor of 10 to the usual default value of 100.’
c) The explanation for factor 10 (line 558) is not logical. It is not the BMDL but the choice of the benchmark dose at 10%. In a similar way, an additional factor of 2.5 is recommended for the T25 approach (that means, for an effect level of 25%). A proposal could be formulated as: ‘A factor of 10 is currently considered to be appropriate to take into account that the effect level for the BMD approach is proposed to be set at 10%. In the same line, if the point of comparison is based .....’
d) It would also be possible to take the ED-01 BMDL instead of ED-10 BMDL as proposed by a Joint Working Party of the SCCP and the Scientific Committee on Health and Environmental Risks SCHER organised by the European Commission, Health and Consumer Protection DG.

Item 3.4 ‘Consideration of the overall margin of exposure’, line 567: In the context of the draft opinion the sentence ‘....that based on the current understanding of cancer biology there are levels of exposure to genotoxic and carcinogenic compounds below which cancer incidence is not increased (biological thresholds in dose-response), however, such levels of exposure

cannot be identified on scientific grounds at the present time' is not very easy to understand and it is not clear why this is explained under item 3.4.

The following special questions have not yet been discussed and should be elaborated in the document:

a) How are epidemiological data on dose effect relationship taken into consideration when calculating the MOE?
b) The categories of genotoxic substances targeted by the proposed strategy should be better defined. It is not clear whether the strategy also covers e.g. substances that cause oxidative DNA damage and whether the MOE approach can also be used for carcinogenic substances for which genotoxic properties only play a minor role in carcinogenicity.
c) There might be a need for further safety factors to cover sensitive groups in the population (e.g. children).
d) Differences in malignity and relevance of the induced cancer for the situation of humans should be considered and could lead to different results of the assessment.