Risiken erkennen – Gesundheit schützen

Risk assessment of genotoxic and carcinogenic substances to be harmonised in the EU

BfR Expert Opinion No. 029/2005 of 18 May 2005

Acrylamide, furan, nitrosamines or polycyclic aromatic hydrocarbons are substances which have been detected in specific foods. Given their properties, these substances constitute a health risk for consumers. Some damage DNA (are genotoxic) and trigger cancer in animal experiments (are carcinogenic). For these substances there is no dose that does not have an effect according to the current level of scientific knowledge. Any amount can be harmful. Ideally, the consumer should not come into contact with these substances at all. In the difficult area of consumer expectations, knowledge, gaps in knowledge and technical viability it is rarely possible to fully meet this demand in the case of foods. Acrylamide is one example for this. The substance is formed during the manufacturing process in a wide range of foods. At present, there are no technologies available to prevent its formation. Given the variety of foods affected, dietary intake recommendations are not an effective approach to protecting consumers either. In cases like this, risk assessors recommend to risk managers that the level of substances in a food category should be reduced to as low as reasonably achievable. This approach is described as the ALARA principle.

In the application of the ALARA principle, risk managers criticise the fact that this approach does not provide any information which enables them to undertake priority-based differentiation. Furthermore, the question has still to be answered as to what is to be considered as "as low as reasonably achievable". A "ranking" of risks would, however, be helpful for risk management when it comes to setting priorities. A harmonised approach to the risk assessment of genotoxic and carcinogenic substances aims to compensate for this "deficit". The European Food Safety Authority (EFSA) has presented a corresponding draft opinion for discussion. The concept takes into account consumer exposure to a specific substance and compares this to the carcinogenic effect of a defined dose in animal experiments. According to EFSA, genotoxic and carcinogenic compounds are to be classified according to their potential risk.

The Federal Institute for Risk Assessment has scientifically evaluated the EFSA draft opinion. BfR welcomes the concept in principle but recommends, amongst other things, using this approach in addition to and not instead of the ALARA principle. If the new approach is applied in isolation, BfR believes there is a risk that the application of the minimisation principle to **all** genotoxic and carcinogenic substances – the current practice - will be undermined. The main points of the evaluation are summed up below. Further details can be found in the English original version of the expert report to EFSA which can also be accessed on our homepage on http://www.bfr.bund.de/cm/208/harmonised_approach_for_the_risk_assessment_of_compounds_which_are_both_genotoxic_and_carcinogenic.pdf and in the EFSA draft opinion [1].

1 Subject matter of the assessment

The European Food Safety Authority (EFSA) has submitted a draft opinion for a harmonised approach for risk assessment of compounds which are both carcinogenic and genotoxic [1]. Comments on this draft opinion will be incorporated into the final version. This is to be discussed in November 2005 at a Scientific Summit of EFSA, the World Health Organisation (WHO) and the International Life Science Institute (ILSI).

The draft opinion lays out the scientifically accepted level of knowledge on carcinogenesis. It formulates a scientifically backed approach for risk assessment of genotoxic and carcinogenic substances.

Up to now risk assessors have normally advised risk managers to use the ALARA principle (as low as reasonably achievable). According to this principle, the level of a genotoxic and carcinogenic substance in a product should be reduced as far as possible with acceptable (technological) efforts. Risk managers had criticised the fact that the recommendation to use the ALARA principle alone does not constitute a foundation in order to set sensible priorities in these activities. In future, this deficit is to be overcome by the calculation of a Margin of Exposure (MOE). The Margin of Exposure results from

a) human exposure (extend of contact with a substance) and
b) the effect dose observed or calculated in an animal experiment for a given tumour incidence.

Compared with the sole application of the ALARA principle, the MOE offers the advantage that based on exposure to genotoxic and carcinogenic substances, the extend of risks can be presented in a comparative manner. In this context, exposure mainly focuses on oral intake with regard to food safety.

The Margin of Exposure is calculated as the margin between two parameters and thereby depicts the relationship between a carcinogenic effect dose, derived from the dose-response curve in animal experiments, and estimated human intake. EFSA considers the dose which leads to a tumour incidence of 10% to be a suitable reference point on the dose-response curve. This is described as the Benchmark Dose Lower Limit (BMDL). The extend of a risk is proportionally the reverse of the Margin of Exposure: if the MOE (the relationship between oral intake and BMDL) is equal to or higher than 10,000, EFSA estimates the existing carcinogenic risk to be low and suggests that these substances be treated with low priority. The more the MOE falls below 10,000 (i.e. the smaller it is), the higher the risk and, by extension, the more urgent the need for minimisation measures.

The 10,000 value for the MOE was not laid down in an arbitrary manner. It results far more from consideration of the following uncertainty factors:

- Factor 100
  a) the difference between animals and man (inter-species difference, factor 10) and
  b) the difference between various human beings (intra-species difference, factor 10);
- Factor 10 for the special variability which extends beyond the variability already obtained in the customarily applied factor 10 for the intra-species difference and concerns the individual cancer risk (depending, for instance, on DNA repair activity and cell cycle control);
- Factor 10 for the fact that the BMDL is not an adequate substitute for a threshold value for tumour induction.

In the event that no viable dose-response data are available for a reliable estimation of the BMDL, it is recommended that the T25 value be used. This value is calculated through a simple rule of three from an effect dose in a carcinogenesis study taking into account control effects and a scaling factor for some species differences. An additional factor of 2.5 is included when using the T25 value for laying down the margin factor (corresponding to a factor of 25,000).

EFSA points out that the use of an MOE of 10,000 or of 25,000 must be societally accepted and that a decision to carry out the resulting risk reduction measures is primarily the responsibility of risk managers.

Concerning the draft opinion for a harmonised approach for risk assessment of compounds which are both genotoxic and carcinogenic, the Federal Institute for Risk Assessment adopts the following scientific position.

2 Result

BfR welcomes the proposed approach because it constitutes an attempt to classify genotoxic and carcinogenic compounds in line with their potential risk for man. In this way, the risk manager has an urgency benchmark for minimising the risk for consumers.

BfR is of the opinion that the MOE approach suggested by EFSA is appropriate in order to present in a comparative manner the risks of genotoxic and carcinogenic substances. BfR, like EFSA, believes that a benchmark approach to determining an effect dose is more appropriate (as long as the corresponding data are available) than the T25 approach also mentioned.

By laying down an MOE of 10,000 and higher, a parameter for a margin of exposure has been recommended for the first time which is deemed to be sufficient. The goal is to indicate a benchmark for existing risks which cannot be completely eliminated from the environment or food and are therefore omnipresent, the level of which has to be critically discussed by society. The Institute consciously refrains from adopting a stance on the question of societal acceptance because this assessment is outside its competences and responsibilities. The derivation of individual factors used for the proposed MOE of 10,000 is, in the opinion of BfR, reasonable from a scientific angle.

The Institute points out that priorities for risk management cannot be set solely by deriving MOE numbers. In each individual case risk assessment must take into account all the findings, particularly concerning differences between species, toxicokinetics and toxicodynamics as well as existing gaps in knowledge. Furthermore, the draft opinion does not clarify whether, and, if so, to what extent possible combination effects of several genotoxic and carcinogenic substances to be found in food have been taken into account. Exposure to structurally related compounds for instance, which each have a specific MOE, can lead to a correspondingly lower MOE for this substance group.

The derivation of an MOE gives risk managers the option of being able to take a decision more easily about what “as low as reasonably achievable” actually means. In principle, however, the ALARA principle – as low as reasonably achievable – should not be challenged and should be used in future, too. This is all the more so the case since an MOE also depends heavily on how safe the exposure assessment is. This largely depends, in turn, on the type and quality of exposure data on which it is based (e.g. nutrition studies).

The EFSA draft opinion does not take into account the fact that there are carcinogenic substances for which genotoxicity only plays a subordinate role for carcinogenesis. In the field of protection at work the “Senatskommission zur Festsetzung maximaler Stoffkonzentrationen am Arbeitsplatz – MAK-Kommission” (Senate Commission for the stipulation of maximum substance concentrations at the workplace) has extended its classification categories for carcinogenic substances. Category 4 includes substances with carcinogenic properties for which, besides the genotoxic effect, there is also a non-genotoxic mechanism of action which is to the fore when it comes to the onset of cancer.

In the EFSA approach the uncertainties attached to the derivation of an MOE, which are due

to the differing quality of the data on which they are based, should be highlighted more.

By way of summary, BfR notes that the proposed procedure can, in principle, be accepted and does generally constitute a good basis for risk assessment along the lines of a comparative consideration of risks. The argumentation should be brought into line with earlier standards particularly concerning common "default values" (see [2] and [3]).

3 Justification

3.1 Margin of exposure

At its 46th meeting (8-17 February 2005) the Joint FAO/WHO Expert Committee on Food Additives adopted a similar procedure to the EFSA Scientific Committee (SC) and derived corresponding MOEs for acrylamide, ethyl carbamate and benzo[a]pyrene, which is considered to be a marker for polycyclic aromatic hydrocarbons. For acrylamide this leads to the lowest MOE and, by extension, the highest priority for minimisation [4].

When undertaking risk assessment in the past, both BfR and its predecessor institutes set the daily intake of man against the effective dose in animal experiments of carcinogenic impurities in foods (cf. [5, 6]).

In the draft of the Scientific Committee a "low health risk" and "a low priority for risk management" are discussed in conjunction with an MOE of 10,000 or higher. From the angle of food toxicology this specific statement is, however, to be questioned at the present time. It is, for instance, not clear whether and, if so, to what extent possible combination effects of genotoxic and carcinogenic compounds have been taken into account. Exposure to structurally related compounds, that have a specific MOE, can lead to the MOE for this substance group being correspondingly lower (e.g. exposure to various nitrosamines, exposure to structurally related methyl eugenol, estragole and safrole).

3.2 Selection of an appropriate point of comparison from the dose-response curve

BfR is of the opinion that a benchmark approach to determining an effect dose is more appropriate (to the extent that the data permit) than the T25 approach also mentioned above. This is because, in the case of the benchmark calculation, the entire information from the dose-response curve can be included in the estimate and the calculation does not just include a point assessment (like for the dose for 25% tumour incidence).

The uncertainty factors (4 x 10) are themselves supported by a substantial database and existing evaluations and have, therefore, been reasonably selected from the scientific angle.

In the draft of the European Chemical Bureau (ECB) for a Technical Guidance Document for the Risk Assessment of Chemicals [7], different methods are presented including the MOE procedure. In addition, the risk extrapolation method is also presented: based on a T25 value, taking into account a scaling factor for some species differences, the cancer risk for man is extrapolated in a linear manner for specific exposures. The latter procedure is used, amongst others, by the Scientific Committee on Consumer Products (SCCP) and is part of the Notes of Guidance [8].

In a joint working group of the Scientific Committee on Health and Environmental Risks (SCHER) and SCCP, the SC opinion was also discussed. Here it was noted, amongst other things, that instead of factor 10 (ED-10 instead of NOAEL) it would have been better to use

the ED-01 BMDL as the substitute for the NOAEL. Moreover, it was explained that there is a direct proportionality between the MOE and the risk extrapolated in a linear manner with the T25 method (for instance MOE 10,000 corresponds to a risk 3.5×10^{-5} in the case of a rat experiment).

3.3 Estimation of human dietary exposure

From the scientific angle the proposal to include only those individuals in the exposure estimation who actually eat a specific food (consumers) and not to extend exposure to the entire population that also includes individuals besides "consumers" who do not eat a certain food (non-consumers) is to be supported. The risks for consumers can thus be assessed in an appropriate manner.

The observation by SC that the various types of nutrition studies supply results which can be used for intake estimates for the assessment of chronic risks is, in principle, correct. However, the various study protocols (for instance 7-day weighing protocol, 24-h recall, diet history method) provide different intake levels reflected in the quantative approach of an MOE. Thus, they have a direct influence on risk assessment. Also the categories of foods are recorded in different ways in the various protocols. Relatively good insight is provided into frequently consumed foods. However, less frequently consumed foods are recorded to differing degrees in the various methods. It is, therefore, possible that foods of this kind will not be depicted at all in a specific type of nutrition study. For that reason attention should be drawn in the SC position to these differences.

3.4 Calculation of the margin of exposure

By calculating this over two variables, i.e. the benchmark for a specific effect size and the benchmark for exposure, the uncertainties are larger than when only one variable is used for characterisation, i.e. the benchmark for the NOAEL or the LOAEL. The same applies to risk assessment with the help of a so-called "unit risk", the estimated value of the risk per dose unit. This indicates which proportionate cancer risk at a dose of 1µg/kg body weight is attributed to lifelong exposure. The use of a unit risk does, however, have one major disadvantage over the MOE. As the unit risk considers the risk of a standardised exposure level, the actual exposure is not included. The risk ranking using a "unit risk" does not, therefore, reflect the real situation. The procedure proposed by SC is, therefore, supported.

4 Management framework/measures

In conjunction with the planning of the new German nutrition study, BfR has already repeatedly pointed out the danger that foods consumed less frequently might not be appropriately depicted.

The question whether an uncertainty factor of 10,000 is societally acceptable and can constitute a limit for risk minimisation measures must – as correctly observed by the SC – be discussed by risk managers.

In the field of product safety (e.g. materials in contact with foods, cosmetics), no risk extrapolation is undertaken. This is currently oriented towards the principles of technical avoidability and minimisation.

BfR points out that the use of the MOE could be linked to a risk that the application of the minimisation principle to **all** genotoxic and carcinogenic substances could be undermined.

The Institute, therefore, believes that the MOE should be used alongside the ALARA principle and not instead of it.

5 References

[1] EFSA draft opinion on a harmonised approach for risk assessment of compounds which are both genotoxic and carcinogenic http://www.efsa.eu.int/advisory_forum/adv_meetings/876_de.html).

[2] WHO/ILO/UNEP International Programme on Chemical Safety Publications “Guidance values for health-based exposure limits. Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits (EHC No 170 (1994))“ http://www.inchem.org/documents/ehc/ehc/ehc170.htm

[3] “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.)

[4] FAO/WHO Expert Committee on Food Additives, 64th meeting, Rome, 8-17 February 2005 (2.1. Acrylamide): ftp://ftp.fao.org/es/esn/jecfa/jecfa64_summary.pdf.

[5] W. Grunow und E.H.F. Schmidt, Bundesgesundheitsblatt 12/90 (1990), 573-577: Ernährungsrisiken durch Schadstoffe

[6] Stellungnahme des BfR zu Sudan I-IV in Lebensmitteln vom 19. November 2003: http://www.bfr.bund.de/cm/208/farbstoffe_sudan_i_iv_in_lebensmitteln.pdf.

[7] Draft of the European Chemical Bureau (ECB) for a Technical Guidance Document for the Risk Assessment of Chemicals. http://ecb.jrc.it/REACH/

[8] Notes of Guidance; Scientific Committee on Consumer Products (SCCP): http://europa.eu.int/comm/health/ph_risk/committees/sccp/documents/out242_en.pdf