Opinion of the Scientific Committee on "A Harmonised Approach for Risk Assessment of Compounds which are both Genotoxic and Carcinogenic"

Comments from the Norwegian Scientific Committee for Food Safety Oslo, 27 May 2005

General comments

The Norwegian Scientific Committee for Food Safety welcomes the EFSA initiative to develop a harmonised approach to risk assessment of exposures to chemicals that are both genotoxic and carcinogenic. The proposed method applying a margin of exposure (MOE) approach, based on the ratio between a benchmark dose (lower 95% confidence limit of a BMD10) in animal experiments and the human exposure, is one way of moving forward in this important area. However, it should be recognised that other approaches are in use, even within the EU. This is not mentioned in the opinion, thus it is difficult to see the proposed method at present as the harmonised approach. It is somewhat surprising that the quantitative approaches used by the European Chemicals Bureau and US Environmental Protection Agency are not mentioned. In these approaches a maximal point estimate of the risk may be calculated by linear extrapolation from a point of comparison, such as the LED10 (US EPA 1996) or the T25 (Dybing et al., 1997).

By using a MOE approach, the opinion avoids giving a point estimate of the risk. However, indirectly the application of a MOE of 10,000 from an incidence of 10% can easily be converted into a risk level of 10^{-5} (or using a MOE of 25,000 from an incidence of 25%). Thus, the present proposal could give the impression of developing the necessary uncertainty factors in arriving at such a risk level *post hoc*, without coming clearly out and saying so. The foundation of the application of the 10 factor each for the uncertainties relating to the carcinogenic process and in particular that the BMDL relates to a small but measurable response, is not very well supported by the arguments and references given in the opinion.

It should be emphasised that the current approach should only be applied when evaluating animal experiments. When human cancer risks are assessed from e.g. large cohort studies, it is probable that inter-individual variation in toxicokinetics and uncertainties in the carcinogenic process already would be reflected in the point of comparison. Thus, an application of a composite uncertainty factor of 100 for human data may in such instances not be valid.

With respect to the discussion whether models reflect the underlying biological process, it should be mentioned, that in the limited number of cases where it is possible to calculate human risks from epidemiological data, there is a very good correlation between human risk values and T25 values from animal experiments (Sanner and Dybing, 2005).

The proposed approach advocates the use of a BMD derived from modelling of dose-response data to arrive at a point of comparison. We in principle support this approach; however, it is seldom that modelling of the current available animal experiments with maximum three dose levels arrive at a sufficiently robust value (IPCS Environmental Health Criteria Document on Principles for Modelling Dose-Response for Risk Assessment of Chemicals, draft 2005). In order to achieve better estimates of the BMD, more dose levels will have to be included. However, this would necessitate a change in the current test guidelines, a process that would take considerable time to complete. The document does not discuss when data allow the use of BMDL modelling. E.g. with a very limited data set not covering a 10 % incidence such modelling would also imply extrapolation into the unknown. Therefore, use of the T25 offers a good alternative to the BMD10 as a point of comparison.

It is not clearly borne out that the application of the 95 per cent lower confidence limit on the BMD10, incorporates an additional uncertainty factor. One could argue that a similar lower confidence limit should be assigned to the T25-values. In a study involving 68 carcinogens covering a range in potency of 10^6, a correlation coefficient of 0.94 was found when both dose descriptors were adjusted to 1 per cent and plotted in a double logarithmic scale. The risks at the same levels of exposure were on average 25 per cent higher with the T25 method than with the LED10 method, showing that within the experimental error the two methods give very similar results (Sanner et al., 2001). Thus, there does not seem to be necessary to apply a 95% lower confidence limit to the T25.

It should also be mentioned that the T25 method as used by the ECB (Sanner et al., 2001) and the LED10 method proposed by US EPA (1996) involves allometric scaling from animal data to calculate a human point of comparison (about x 7 from mice to humans, about 3.5 x from rats to humans.

The opinion does not address the situation of data selection for calculation of the point of comparison when results from more than one carcinogenicity study are available. We would advocate the selection of the study with the most sensitive outcome, i.e. with the lowest point of comparison, as a default position when there is no information that could guide the selection.

The document is unclear with respect to the use of the descriptor 'genotoxic'. For instance, in lines 104-106, the term is used for those compounds providing positive results in different test systems *in vitro* and *in vivo*. Those carcinogens that show evidence of DNA reactivity *in vivo*, are stated to presumably not show a dose threshold. However, in lines 110-113, for some genotoxic agents threshold-based mechanisms are said to be conceivable. In addition, other compounds may show indirect DNA reactivity, e.g. through oxidative stress (Klaunig and Kamendulis, 2004). The use of the term 'genotoxic' should therefore be defined and/or referenced. Perhaps it will be necessary to use a term such as 'directly DNA-reactive genotoxic' or 'non-threshold genotoxic' throughout the document to be more precise with respect to what is meant by the descriptor.

Specific comments

Throughout the document: Use 'BMDL10' rather than 'BMDL' when referring to a BMR of 10%.

Line 243, Figure 1: This figure gives an incorrect impression of the current status of the use of mathematical modelling in carcinogen risk assessment. Models such as the Probit, Logit, Weibull and One Hit models are obsolete and without foundation in understanding of the carcinogenic process. Showing these models in the figure gives the impression that these models are among those used in carcinogenic risk assessment. Currently, biological based models such as the multistage model are in use, this has been shown to give very similar results as the application of a linear extrapolation from a point of comparison (Sanner et al., 2001)

Lines 440-443: This statement does not necessarily hold true if there is a clearly defined subgroup with a markedly different intake than the rest of the population.

Lines 564 and 592: The number should be 25 and not 2.5 (25 from the T25 is used instead of 10 from the BMDL10).

Line 620: Add 'or 25,000 or higher, based on the T25' after '10,000 or higher, based on the BMDL10' since the use of the T25 approach is presented as an alternative to the BMDL10 in Section 3.4.

Assessed by

Ad hoc working group: Erik Dybing (Chair), Tore Sanner, Jan Alexander, Helle Knutsen, Edgar Rivedal

Scientific Committee: Åshild Krogdahl (Chair), Bjørn Næss, Hilde Kruse, Erik Dybing, Ingolf Nes, Jan Alexander, Janneche Utne Skåre, Anne Kathrine Haldorsen, Martinus Løvik, Wenche Farstad, Lene Frost Andersen, Georg Kapperud, Øyvind Lie, Judith Narvhus, Leif Sundheim

Scientific coordinator from the secretariat: Tor Øystein Fotland

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