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COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COC Response to Draft Opinion of EFSA Scientific Committee on a Harmonised Approach for Risk Assessment of Compounds which are both Genotoxic and Carcinogenic

Members were asked for comments in April on this draft opinion, which was out for public consultation. The text of the response subsequently submitted on behalf of the committee is attached, for information. (The response had to be entered onto a form on the EFSA website and therefore could not be sent as a letter from the Chairman).

Secretariat
June 2005

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EFSA Scientific Committee Opinion on “a Harmonised Approach for Risk Assessment of Compounds which are both Genotoxic and Carcinogenic”

I am responding on behalf of the Committee on the Carcinogenicity of Chemicals in Food, Chemical Products and the Environment (COC) to the public consultation on the above opinion. The COC welcomes the opportunity to comment on this advice from the EFSA Scientific Committee.

Members of the COC have made a number of detailed comments on the advice and these are attached. However, the committee also has a more general concern about the opinion. It is not clear whether the EFSA scientific committee intends, in future, that the margin of exposure approach, as laid out in the document, should replace the ALARP approach for *all* food chemicals which are both genotoxic and carcinogenic or only for specific categories or in specific situations. For example, would the EFSA Scientific Committee recommend that it be used if an application was received for a new pesticide which was both genotoxic and carcinogenic if the residues found in food result in a Margin of Exposure well above 10,000? The COC recognises that, ultimately, the action to be taken on any chemical is a matter for risk managers who must take into consideration issues other than risk but, in our experience, the advice from a risk assessment committee is highly influential in any risk management consideration. The COC reiterates its view, as stated in its 2004 Guidelines, that, because of the many uncertainties, a threshold approach should not currently be used as a generic approach for genotoxic carcinogens. This may also be the view of the EFSA Scientific Committee but, if so, it is not clear from the draft opinion and it is suggested that you redraft the conclusions to give a clearer indication of the situations in which you foresee this approach being applied and to be more explicit about the principle of ALARP.

COC members have also suggested that the opinion would benefit from some worked examples of known carcinogens. This would help to demonstrate how the methodology would be applied in practice.

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Detailed comments from COC members on the EFSA opinion

1. L105. Underpinning any discussion on genotoxic carcinogens is the need for a conclusion regarding genotoxicity. Is there an EFSA approved strategy for assessing genotoxic potential that can be referenced in the document? DNA reactivity *per se* needs to be qualified, as this is not generally accepted as sufficient evidence of genotoxicity.
2. L141. Progress in identifying carcinogen-specific mutational patterns in oncogenes and tumour suppressor genes in animal tumours has not been as great as it once appeared it might be. This is presumably because there are other targets for genotoxins (e.g. affecting genome stability).
3. L186-189. The idea that linear extrapolation from high doses can lead to overestimation of true risk is a possibility. However, the opposite can also be true. Vineis *et al* (International J Cancer, 2004) observed plateauing of the risk of bladder cancer at high doses of tobacco, with a plausible biological explanation. The same has been observed repeatedly in biological cohorts. This would result in underestimation of the risk from linear extrapolation.
4. L200-208. Hormesis is a hypothesis, not a theory i.e. there is no proof that it exists. Therefore, perhaps it would be better to exclude this paragraph. Moreover, even if the J-shaped curve did exist, in the absence of any means of defining the shape of the curve at human exposure levels, it is better to overestimate risk than to underestimate it.
5. L217. For most common tumour types induced in animals, the background incidence is not zero and, indeed, can be quite substantial in some cases, further reducing study power.
6. L238. Low dose extrapolation is often a two-stage process. The first is to fit a curve to the experimental data to allow selection of a point of departure within the range of the data. The second is to choose a means of extrapolating to human exposures, which is generally where the types of curve discussed are used. It should also be noted that the US EPA has now abandoned the choice of multiple models and recommends a simple linear approach (see EPA final Cancer Guidelines, issues April 2005).
7. L256. If one were to use linear extrapolation in all cases where a threshold cannot be assumed, this would overcome many of these reservations.
8. L364. The COC in its Guidelines (2004) identified several potential problems in using either the TD50 or the T25 as the basis for quantitative risk assessment of diverse chemical carcinogens. Their value was seen in comparing structurally related compounds.
9. L385. Whilst any curve may be used to obtain an estimate of the BMD, the issues in model and error function selection are extremely complex (see draft report of IPCS Dose-response workshop, 2004). The statistical issues need to be recognised.

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10. L488. The suggestion that a default factor of 100 for inter- and intra-species differences would be sufficient for genotoxic carcinogens is a novel proposal and appears to confuse threshold and non-threshold approaches. In a non-threshold approach it is not possible to estimate a dose without risk, the usual basis for applying the default factor. As an alternative, one attempts to estimate a dose that poses a risk considered acceptable to the risk manager. This is typically a very low number (e.g. 1 in 100,000 or less). Application of a 100-fold default would not reduce the risk to anywhere near this level (see also below). If one uses a 100-fold default factor analogous to that used for non-cancer risk assessment, one must assume that it can be subdivided into kinetic and dynamic components, leaving the option to modify the factor by compound-specific data, e.g. on the enzymes of activation and detoxication.

11. L 541. The paper by Palli is, in fact, *in vivo*, not *in vitro*.

12. L551. The BMDL is not the same as the BMD as it is numerically often equivalent to the NOAEL. Perhaps more importantly, when the BMDL is used as the basis for risk assessment of non-genotoxins, the normal 100-fold default is used. If it can be argued here that the BMDL represents a response and hence an additional factor is required, this has important implications for the risk assessment of non-carcinogenic compounds.

13. L 567-570. If a threshold cannot be demonstrated then, scientifically, it cannot be known whether it exists or not. Perhaps it would be better to say: “The Scientific Committee concludes that.....there are likely to be levels of exposure....”

14. L572. In using the MOE for ranking carcinogens and priority setting, some implicit assumption will be needed regarding the extrapolation model. It is likely that most will (implicitly or even sub-consciously) adopt a linear extrapolation model, that is that a compound with an MOE of 1000 is of approx 10 times greater concern than one with an MOE of 10,000. If a linear model is not assumed, what relationship will be assumed. If hockey stick-shaped, then ranking of compounds with high MOEs would be different than for those with low MOEs. For example, the difference in potency of compounds with MOEs of 1000 and 2000 might be substantial whilst for compounds with MOEs of 20,000 and 100,000 there might be little difference. This complication means that the most likely outcome will be the implicit assumption of linearity.

15. L585. Partitioning the MOE for a genotoxic carcinogen in this way is, we believe, unprecedented, and also unjustified for the reasons given above. It implies that, with suitable additional information on variability in cancer-related processes and on inter- and intra-species differences in kinetics and dynamics, it would be possible to reduce the MOE considered acceptable, possibly by a substantial amount. It is the margin of 10,000 or above that is considered a pragmatic minimal risk level. Any erosion of this has different implications from that with a non-carcinogen, if one assumes no threshold for genotoxins.

16. L 663. The editor is P Vineis, not W Ryder.