

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

CC/06/20

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

**COMPARATIVE RISK ASSESSMENT: APPLICATION OF THE MOE
APPROACH FOR COMMUNICATING THE RISKS OF EXPOSURE TO
GENOTOXIC CARCINOGENS**

I. Background

COC discussion on Comparative Risk Assessment (CRA)

1. The COC has previously discussed proposals for the CRA project, which sought to communicate better the carcinogenic risks potentially associated with unavoidable environmental exposures to carcinogens. At the July 2006 meeting, three possible approaches were examined. These were: Sir Kenneth Calman's Risk Scale, Paling Perspective and Dr Frank Duckworth's Riskometer. Comments from COM Members and a further additional approach developed by the National Radiation Protection Board (NRPB) were also discussed.
2. The COC endorsed the COM's suggestion that a risk professional should be invited to advise on how we could develop the CRA project and improve the communication of risk associated with exposures to carcinogens.
3. During the discussion at the July meeting, the FSA asked whether the COC could comment on the potential usefulness of the Margin of Exposure (MOE) approach being developed by the European Food Safety Agency (EFSA), the World Health Organisation (WHO) and the International Life Sciences Institute (ILSI) as a way of prioritising the risks associated with unavoidable exposure to genotoxic chemical carcinogens in food. The MOE is the numerical value obtained by dividing a reference point on the dose response curve for carcinogenicity in experimental animals by estimated human exposure to the chemical. The committee agreed that this approach, which was essentially consistent with the Minimal Risk Level (MRL) approach outlined in the current COC guidance (COC, 2004), would be worth developing. It had been used by the Joint Expert Committee on Food Additives of the Food and Agriculture Organisation and the WHO (JECFA) for advising on risks of compounds that are both genotoxic and carcinogenic (JECFA, 2005). Therefore, it might also be extended for CRA.
4. This paper develops the MOE approach. It contains a summarised report of a recent EFSA/WHO/ILSI conference (Barlow et al, 2006) which discusses the use of the MOE approach for the risk assessment of substances that are genotoxic and carcinogenic. A copy of the report is appended in Annex 1.

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

5. The paper also attempts to develop a method for defining bands of MOE, which could improve the public presentation of committee advice on genotoxic carcinogens.

6. The final part of this paper presents comments from Professor Lynn Frewer, from Wageningen University, The Netherlands, who has agreed to participate and discuss the feasibility of the current proposals.

II. Barlow et al. (2006). Risk assessment of substances that are both genotoxic and carcinogenic. Report of an international conference organised by EFSA and WHO with support of ILSI. Food Chem Toxicol, Vol 44(10): 1636-50.

7. This paper is the report of a joint EFSA/WHO/ILSI Europe conference, which was held in November 2005 to discuss the advantages and disadvantages of the various approaches available to characterise the risks associated with exposure to genotoxic carcinogens in food.

8. The following three papers were used as the basis for discussions at the conference:

a. J O'Brien et al. (2006). Approaches to the risk assessment of genotoxic carcinogens in food: a critical appraisal. Food & Chem Tox, Vol (44):1613-35 (in press at the time of the conference).

b. EFSA (2005). Opinion of the EFSA Scientific Committee related to a harmonised approach for the risk assessment of substances which are both genotoxic and carcinogenic (the COC submitted comments on the draft of this opinion in 2005).

c. JECFA (2005). Summary and conclusions of the 64th Meeting of the Joint FAO/WHO Expert Committee on Food Additives.

9. All three documents considered use of the NOAEL to be inappropriate for the risk characterisation of DNA reactive genotoxic carcinogens and that the Margin of Exposure (MOE) approach was the most scientifically credible approach to use. They all favoured the use of the lower limit of the confidence interval on the benchmark dose¹ (BMD) as the reference point with which to compare intakes, while noting that the T₂₅ could be used in cases where the dose-response data were not adequate to define the BMD or the lower limit of its confidence interval of the (BMDL).

10. All three papers addressed only dietary exposure to genotoxic carcinogens and considered MOEs in terms of providing advice to risk managers, rather than for CRA purposes. In this context, they all agreed that intakes should be provided for different percentiles of the general population

¹ The Benchmark Dose (BMD) is the dose which causes a specific response (a Benchmark Response (BMR) – for example, 5% or 10%) above the control incidence.

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

and for any subgroups with higher intake patterns. This means that there will be a range of MOE values for the same substance.

11. Barlow et al (2006) also highlights several important areas that were not addressed by any of the papers. These include:
 - a. an agreed strategy for assessing genotoxicity;
 - b. developing an approach for compounds for which it is not possible to identify a BMDL or T_{25} ;
 - c. whether the MOE approach would be useful for the risk assessment of proven human carcinogens;
 - d. understanding that, regardless of the MOE value, ALARA/P approaches (see below) should always be considered to reduce exposure to genotoxic carcinogens;
 - e. addressing the fact that uncertainties also exist in the intake (exposure) estimates (and not just in the dose-response) which will affect the MOE value.

12. Issues raised by the different approaches to assessment of genotoxic carcinogens were discussed at the conference. These tools were:
 - the ALARA/P approach
 - low-dose extrapolation of data from rodent carcinogenicity bioassays
 - threshold of toxicological concern
 - margin of exposure

13. The advice given to risk managers in the past has generally been that exposures of genotoxic carcinogens should be kept as low as reasonably achievable or practicable (ALARA/P). This approach requires the least information since it is based only on hazard identification. The approach makes no use of any dose-response data and tends to treat the risk from all genotoxic carcinogens as equal, thus making it difficult for risk managers to prioritise or interpret the advice in terms of current exposures. It can also create problems for risk communication; because it provides only a simple qualitative message about genotoxic carcinogens, it is difficult to convey that some substances may be more hazardous than others, either because of their potency or because of the exposure levels. However, in data-poor situations, it may only be possible to give advice to risk managers that exposure should be ALARA/P.

15. Although there were several limitations associated with the use of the MOE approach, there was a consensus at the conference that it was the preferred approach for risk characterisation. The reasons for this conclusion are listed in section 3.2.2 of Barlow et al. (2006). In brief, these relate to using and providing more information than the simplistic advice that exposure should be ALARA or below a threshold of toxicological concern, whilst avoiding the many limitations of extrapolation to risk at low doses, which have previously been discussed by COC (2004).

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

16. The conference agreed that the choice of the most appropriate reference point for calculating the MOE should be determined by the extent and quality of data:

<u>Reference point^a</u>	<u>Criteria</u>
BMDL ₁₀ ^b	If there are sufficient data available to enable a BMDL to be determined
T ₂₅	If data is insufficient to derive a BMDL ₁₀

a: For information on the calculation of the T₂₅ and BMDL₁₀, see Annex 2.

b: The lower confidence interval of the dose which causes a BMR of 10% tumour incidence above the control incidence. A benchmark response of 10% was preferred to a 5% increase in tumour incidence, because modelling of lower incidences generally results in greater uncertainties.

17. The conference concluded that the MOE approach was considered the a useful and pragmatic approach for comparing and prioritising different genotoxic carcinogens especially if accompanied by a narrative description of the inherent uncertainties in the calculation.

18. Delegates proposed further discussions of the MOE approach as a way forward, including suggestions on how to make technical improvements in the risk assessment of substances that are both genotoxic and carcinogenic. Key issues requiring further discussion/research were:

- Harmonisation of the MOE approach with respect to criteria to assess adequacy of data, dose-response modelling options, deciding on how/what reference point to derive and which models and software to use
- Development of adjustment factors to compensate for incomplete data e.g. allows MOEs derived from T₂₅ to be compared with MOEs derived from a BMDL₁₀
- Guidance for risk managers
- Risk communication of MOE
- Research that investigates consistency between MOEs obtained from animal bioassay data with those obtained from human epidemiological data.

III. Worked examples

19. The following section presents some examples of MOEs which have been calculated for a number of dietary genotoxic carcinogens. These are presented for illustrative purposes only.

20. O'Brien et al (2006; attached at Annex 3) calculated MOE values for the following 5 genotoxic carcinogens present in food: acrylamide, aflatoxin-B1, benzo[a]pyrene (BaP), dimethylnitrosamine, ethyl carbamate and PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine) (Table 3).

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

Table 3. Margins of exposure (MOEs) for selected foodborne carcinogens (from O'Brien et al, 2006)

Carcinogen	T25 mg/kg bw/d	BMDL10 ^a mg/kg bw/d	Estimated Human Exposure ^b ng/kg bw/d	MOE	
				T ₂₅	BMDL ₁₀
Acrylamide	0.65	0.31	410 (males)	1600	760
			420 (females)	1600	740
			430	1500	720
			920	710	340
			2310	280	130
Aflatoxin B ₁	0.5 x10 ⁻³	0.16 x10 ⁻³	0.25	2000	640
			0.3	1700	530
			2.0	250	80
B[a]P	2.4 ^c	2.0	10-15	160000- 240000	130000- 200000
Dimethylnitrosamine	0.15	0.06	14 ^d	11000	4300
Ethyl carbamate	1.0	0.28	20	50000	14000
			70	14300	4000
			2000	500	140
PhIP	2.0	1.25	4.8-7.6	260000- 420000	170000- 260000

^aModels assumed a maximum response of 100% at high doses with the exception of DMN where the response was seen to plateau at an incidence of approx 70%

^bAs intake from food

^cNon-linear response

^dComposite intake of N-nitrosodimethylamine and N-nitrosopyrrolidine

21. The paper emphasises that the quality of raw data used to generate the above MOE values has not been evaluated and the figures are for illustrative purposes only.

22. JECFA calculated the MOEs for acrylamide, ethyl carbamate and for polycyclic aromatic hydrocarbons (PAH) in 2005 (see http://www.who.int/ipcs/food/jecfa/summaries/summary_report_64_final.pdf) and for 1,3-dichloro-2-propanol (1,3 DCP) in 2006 (<http://www.who.int/ipcs/food/jecfa/summaries/summary67.pdf>). These are summarised in Table 4. The values for benzo(a)pyrene differ from that in Table 3 due to differences in the exposure data used.

Table 4 Margins of exposure (MOEs) for selected foodborne carcinogens (from JECFA, 2005 and 2006)

Carcinogen	BMDL ₁₀ used (mg/kg bw/day)	Estimated human intakes used (ng/kg bw/day)	MOE
Acrylamide	0.3	1000 (average intake) 4000 (high intake)	300 75
Ethyl carbamate	0.3	15 (food) 80 (food plus alc bevs)	20,000 3,800
PAH (using BaP as a marker)	0.1	4000 (mean intake) 10,000 (high intake)	25,000 10,000
1,3 DCP	3.3	51 (mean intake) 136 (high intake)	64,000 24,000

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

IV. Developing an MOE based approach to aid the presentation of risk advice to the public

23. As noted above, the MOE approach is essentially consistent with the Minimal Risk Level (MRL) approach outlined in the current COC guidance (COC, 2004). The guidance states:

"...under certain specific circumstances, for example very low exposures to genotoxic carcinogen contaminants or impurities, a pragmatic minimal risk level for these compounds may be identified. A minimal risk level for a genotoxic carcinogen contaminant or impurity is defined within this document as an estimate of daily human exposure to a chemical identified by expert judgement that is likely to be associated with a negligible risk of carcinogenic effect over a specified duration of exposure (usually a lifetime)"..."The derivation of the minimal risk level for a genotoxic carcinogen contaminant or impurity involves assessment of all available carcinogenicity dose-response data to identify an appropriate dose without discernable carcinogenic effect, or the lowest dose tested, if effects are apparent at all doses, and the use of expert judgement to derive an appropriate margin of exposure. One proposal is that the maximum upper limit for the margin of exposure for carcinogenicity might be 10,000 (Gaylor, 1999; Gold et al, 2003)."

24. More recently, organisations such as JECFA and EFSA have made proposals about the interpretation of the magnitude of a MOE. EFSA (2005) considered that an MOE of 10,000² or higher was of low concern from a public health point of view, which could be translated as a low priority for risk management actions, although the view has been expressed that it is important that the figure of 10,000 should not be viewed as some kind of threshold for triggering concern or risk management action. Furthermore, a high MOE should not preclude consideration of taking risk management action, including the application of ALARA/P.

25. Similarly, JECFA (2005), whilst avoiding defining 10,000 as a cut-off, described MOEs of 10,000 and above as "of low concern for human health", whereas smaller MOEs were described as "of concern". JECFA concluded that the acceptability of an MOE is a risk management decision, but that risk assessors could give guidance on its adequacy taking into account the inherent uncertainties and variability.

26. O'Brien et al (2006) documents the Canadian Food Regulatory Agency's use of a risk characterisation tool called the Exposure Potency Index (EPI)³, which is regarded as the reciprocal of the MOE (Health Canada,

³ Defined as the average exposure in the population divided by the dose in experimental animals that produces a 5% incidence of tumours

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

1994). It is used to help present EPI values as bands for risk management action.

EPI band	MOE band equivalent	Priority status
$\geq 2 \times 10^{-4}$	< 5000	High Priority
$2 \times 10^{-4} - 2 \times 10^{-6}$	5000- 500,000	Moderate Priority
$< 2 \times 10^{-6}$	> 500,000	Low Priority

NB. Health Canada, 1994 do not provide an explanation for the basis and derivation of these values

27. This suggests that it may be possible to present MOE values in a similar way for risk communication to the wider public i.e. to help the public to better understand the risk of different carcinogen exposures. **The FSA**

28. The FSA has proposed that the approach could be expanded (on a pragmatic basis) to a banding of the MOE for use in communicating risk to the public, for example, as shown below:

MOE Band	Interpretation
<10,000	possible concern
10,000-1,000,000	low concern
> 100,000	negligible concern when action is being taken to further minimise future exposure
> 1,000,000	negligible concern

29. At the time COC evaluates carcinogenicity of specific compounds, exposure data are often not available, and so an MOE cannot be calculated. However, if COC identified an appropriate reference point on the dose-response relationship, the FSA could use this to calculate an MOE when exposure data became available in order to provide information to consumers underpinned by COC advice. It is stressed that this is for communication purposes and a large MOE should not be a basis for condoning illegal use of genotoxic carcinogens in food.

V. Comments from Professor Lynn Frewer

30. Professor Lynn Frewer, from Wageningen University, The Netherlands has agreed to comment on our current proposal re: use of the MOE approach for risk evaluation of genotoxic carcinogens. She has expertise in developing and testing models of communication of risk in relation to food, and is also interested in investigating the dynamics of the risk characterisation procedures.

31. It is hoped that Professor Frewer will be able to attend the meeting and, if not, that her comments will be available for tabling.

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

V. Questions for the Committee

32. The Committee is asked to address the following questions:

- Members are asked for views on the principle of using the MOE for prioritising risk of exposure to genotoxic carcinogens.
- Members are asked to comment on the feasibility of banding MOE values based on the approach proposed by the FSA for the presentation of advice to wider audiences.
- If Members consider that the banding approach would be useful, what are their views on the banding proposal in paragraph 28? Are there other interpretations of the numerical values which could be used which would aid communication of risk to the public (for example, the public may not distinguish between “low” and “negligible” concern).
- Do Members support extending the use of the MOE and banding approach to genotoxic carcinogens which are environmental contaminants? If so, which ones might be considered?

Secretariat, November 2006

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

References

1. Barlow et al. (2006). Risk assessment of substances that are both genotoxic and carcinogenic. Report of an International conference organised by EFSA and WHO with support of ILSI Europe. Food Chem Toxicol, Vol 44(10): 1636-50.
2. COC (2004). Minimal Risk Levels for genotoxic carcinogen contaminants and impurities. In: Guidance on a strategy for the risk assessment of chemical carcinogens. Committee on Carcinogenicity of chemicals in food, consumer products and the environment, Department of Health.
http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4091206&chk=EKzpk6
3. EFSA (2005). Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic
http://www.efsa.europa.eu/en/science/sc_commitee/sc_opinions/1201.html
4. EPA (2006). Benchmark Dose Software (BMDS) Tutorial. Application of BMDS: Cancer Bioassay Data.
http://www.epa.gov/ncea/bmds_training/application/appl.htm
5. Health Canada (1994). Human Health Risk Assessment for Priority Substances. Environmental Health Directorate, Health Canada, Canada Communication Group – Publishing, Cat No En40-215/41E, Ottawa
6. JECFA (2005). Summary and conclusions of the 64th Meeting of the Joint FAO/WHO Expert Committee on Food Additives. JECFA/64/SC
http://www.who.int/ipcs/food/jecfa/summaries/summary_report_64_final.pdf
7. Kroes et al (2004). Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem Toxicol. 2004 Jan;42(1):65-83
8. O'Brien et al. (2006). Approaches to the risk assessment of genotoxic carcinogens in food: a critical appraisal. Food & Chem Tox, Vol (44):1613-35

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

Annex 1 to CC/06/20

Barlow et al. (2006). Risk assessment of substances that are both genotoxic and carcinogenic. Report of an International conference organised by EFSA and WHO with support of ILSI Europe. Food Chem Toxicol, Vol 44(10): 1636-50.

For copyright reasons the contents of this annex will not be included when this paper becomes publicly available. The bibliographic details of the annexed material are given above. The document is in the public domain and individuals can obtain it by application to appropriate sources.

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

Annex 2 to CC/06/20

Calculating the T25

1. T25 is defined as the chronic daily dose, which will give tumours in 25% of the animals (above background incidence) at a specific tissue site.
2. T25 is calculated as follows:
 - Linear extrapolation of the lowest dose that gives a statistically significant increase in tumours (the critical dose).
 - A formula is then used to derive the T25 value:

$$C = [(B/100-A/100)/(1-A/100)] \times 100$$

$$T25 = (25/C) \times 100$$

Where:

- A = proportion of animals with the tumour in the control group (%)
- B = proportion of animals with the tumour in an exposed group (%)
- C = net increase in tumour frequency (%)

Calculating the BMDL₁₀

1. The EPA provides benchmark dose software that can be downloaded from the internet free of charge, and allows application of a range of different mathematical models. http://www.epa.gov/ncea/bmds_training/index.htm
2. A number of reporting requirements are required to help judge whether or not the choice of studies and endpoints for modelling has been done appropriately and whether the most appropriate BMD and BMDL have been selected as the POD for low dose extrapolation (EPA, 2006)
3. The EPA provides a worked example for calculating the BMDL from cancer bioassay data (using a default model) (http://www.epa.gov/ncea/bmds_training/application/appl.htm).

This is a draft paper for discussion. It should not be quoted, cited or reproduced.

Annex 3 to CC/06/20

O'Brien et al. (2006). Approaches to the risk assessment of genotoxic carcinogens in food: a critical appraisal. Food Chem Toxicol, Vol (44):1613-35

For copyright reasons the contents of this annex will not be included when this paper becomes publicly available. The bibliographic details of the annexed material are given above. The document is in the public domain and individuals can obtain it by application to appropriate sources.