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

STATEMENT ON THE COT WORKSHOP ON EVOLVING APPROACHES TO CHEMICAL RISK ASSESSMENT

Introduction

1. On 7th February 2007 the Committee held an open workshop on "Evolving Approaches to Chemical Risk Assessment". This workshop was designed to explore in more detail some of the approaches described in the Committee's report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment (COT 2007), which has now been published.

2. Invited expert speakers made presentations on techniques that the Committee may wish to exploit in future risk assessments. Members participated in discussions during the workshop and subsequently. This statement summarises the presentations and Committee's discussions.

Presentation Summaries

The Benchmark Approach[a]

3. The Benchmark dose (BMD) is defined as the dose associated with a pre-specified (small) effect size (Crump 1984). It is estimated from a statistical model fitted to the dose-response data. To take the statistical uncertainties in the data into account, a confidence interval around the BMD is calculated. The lower 95% confidence limit is often termed the BMDL. The BMDL may serve as a Reference Point (RP), or Point of Departure (PoD) for deriving a health-based guidance level for human exposure; e.g., Acceptable Daily Intake (ADI), Tolerable Daily Intake (TDI) or Reference Dose (RfD).

4. Dose-response data can be described by a model where the dose-response parameters are simply the observed frequency of responses (in the case of quantal data), or the observed average responses (in the case of continuous data) at each dose group. In this "saturated" or "full" model the number of parameters is equal to the number of dose groups. The

[a] BMD software was demonstrated during the presentation.

aim of dose-response modelling is to replace the observed dose-response data with a smoother curve, produced by a dose-response model that contains fewer parameters than the number of dose groups. On the other hand, the dose-response model should still give an adequate description of the observed dose-response, i.e. the number of parameters should not be too small. Thus, the aim is to find a dose-response model containing the minimum number of parameters that still results in a satisfactory description of the dose-response data.

5. In practice, different models with the same number of parameters can often be found that all give a satisfactory fit to the same data. In the BMD approach the BMD(L)s are calculated for all acceptable models, resulting in a range of values. The range of BMD(L) values (partly) represents the uncertainty regarding the real shape of the dose-response, and is sometimes termed 'model uncertainty'. For data that are relatively poor (e.g., few dose groups, few animals, large scatter), the range of BMDL values will tend to be wider than for data that are relatively good (e.g., many dose groups, many animals, small scatter).

6. The available software allows the BMD approach to be applied without detailed statistical knowledge: the BMDS developed by the US Environmental Protection Agency (EPA), and Proast developed by the National Institute for Public Health and the Environment in the Netherlands (RIVM). These institutions have agreed to make both packages as consistent as possible, so that the outcomes from a dose-response analysis would not depend on the software applied (as long as the same assumptions are used). The BMDS software can be downloaded from the EPA website and is easy for the non-expert to use[b] . The Proast software needs to be implemented in a statistical software environment (*S-plus* is a commercially available software package or *R* is a free alternative available under a GNU General Public License[c]) and some basic knowledge in use of S-plus or R is required to access the Proast software. The advantage of Proast is that it contains more options than BMDS, for instance the inclusion of covariates (e.g. sex) in the modelling, bootstrapping and fitting non-monotonic models. Finally, Proast allows for probabilistic hazard characterisation.

Probabilistic exposure assessment modelling

7. The purpose of probabilistic methods in risk analysis is to quantify variability and uncertainty, so that it may be taken into account in a risk assessment. Variability is real variation in factors that influence exposure and effects, e.g. dietary differences between individuals, whereas uncertainty is caused by limitations in our knowledge of factors that influence exposure and effects, e.g. chemical concentrations that are too low to be quantified. It is important to separate variability and uncertainty

[b] http://www.epa.gov/ncea/bmds.htm
[c] http://www.r-project.org/

in risk assessment because they have different implications for risk management: variability determines the frequency and severity of effects, e.g. what proportion of the population will experience a sublethal effect, whereas uncertainty determines the accuracy and precision of our assessment, i.e. how sure we are. It is usually desirable to keep variability and uncertainty separate. This may be achieved by hierarchical simulation (2-dimensional Monte Carlo) or hierarchical analysis.

8. Variability in exposure is often expressed by estimating a percentile from distribution of exposures in the population, while the most familiar expression of uncertainty is a confidence interval. Thus one possible output from a probabilistic exposure assessment is an estimate of the 97.5^{th} percentile exposure, together with its 95% confidence interval.

9. Dietary exposure to a chemical in food depends primarily on the frequency and amount of contaminated food that is consumed, the concentrations of chemical in the food, and body weight (because exposure is expressed relative to body weight). Body weight and food consumption vary between individuals, and concentrations vary between food items. Deterministic exposure assessments do not attempt to quantify these sources of variation; instead they provide a single, usually conservative, estimate of exposure from selected values for consumption, concentration and body weight. This can be an effective tool for screening assessments but does not describe the variation of exposure in the population.

10. Probabilistic methods quantify variation in exposure, by using distributions to describe variation in consumption, concentration and body weight, then combining these to produce a distribution for exposure. The most commonly-used methods for this are bootstrapping and Monte Carlo simulation, and software for this has been developed by several organisations. Typically, these programs use data on consumption and body weight from dietary surveys, and combine them with distributions for concentration. Recently, Wout Slob (2006) has argued that this type of procedure is inadequate because it does not separate different types of variation affecting consumption: variation in the frequency of consumption (e.g. proportion of days when potatoes are eaten) and variation within and between individuals in the amount of consumption (e.g. amount of potatoes eaten). He proposed that for many (but not all) types of exposure assessment it would be preferable to use statistical models to describe variation in frequency and amount of consumption, rather than performing calculations directly with the survey data. Depending on the situation (acute or chronic assessment, and daily or less frequent intakes), the statistical models can either be used on their own or as an input to Monte Carlo simulation. In either case, the output is a distribution describing the variation of exposure.

11. Exposure assessment may be affected by many uncertainties including measurement and sampling uncertainties affecting concentrations, consumption and body weight, uncertainty about the choice of parametric distributions to describe variability, uncertainties about extrapolations used

to cover data gaps, uncertainty about model structure, uncertainty about correlations or dependencies between inputs, differences in expert opinion, excluded factors, and ignorance (the possibility that unknown factors may influence exposure). Examples from different areas of exposure assessment (e.g. pesticides, packaging, etc.) have recently been reviewed in an opinion of the European Food Safety Authority (EFSA 2006).

12. The presentation illustrated some of these approaches using a practical example concerning the acute exposure of children to carbendazim in apples and apple products. Interest in this example arose from a previous modelling study by Pennycook *et al*. (2004). Bayesian methods were used to model measurement and sampling uncertainties affecting concentration data, and this was combined with survey data on consumption and body weight.

13. It is neither practical nor necessary to quantify all uncertainties. However, it is essential to consider all identifiable uncertainties at least in a qualitative way, and evaluate their potential impact on the assessment outcome, so that this can be taken into account in decision-making (risk management). The EFSA (2006) opinion proposed a tiered approach in which uncertainties are initially considered qualitatively, with the option of progressing to sensitivity analysis or probabilistic modelling for the most influential uncertainties if this appears necessary to enable risk managers to reach a decision.

14. Until now, probabilistic approaches have generally been applied to individual exposure assessments, usually for a single chemical. Another important application of probabilistic approaches is to assist in the calibration of the procedures used in deterministic screening assessments. Although screening procedures are designed to be conservative, the level of protection they offer is generally unknown. This can be estimated by comparing deterministic screening calculations either to direct measurements of exposure (e.g. duplicate diet studies) or to probabilistic estimates of exposure. The EFSA opinion on the IESTI (International Estimate of Short Term Intake) equation, which is used in acute exposure assessment of pesticides, has now been adopted and will be published on their website in due course[d].

Probabilistic approaches to hazard characterisation and integrated probabilistic risk assessment

15. Although probabilistic approaches in risk assessment have mainly related to exposure assessment, they have also been developed for hazard characterisation. Briefly, uncertainty or assessment factors (AF) are applied not as single numbers (such as 10 or 3), but as (statistical) distributions. These AF distributions reflect the fact that each type of factor

[d] http://www.efsa.europa.eu/en.html

(e.g. inter-, or intraspecies, subchronic-to-chronic) is not a constant, but varies among chemicals. The challenge is to estimate these distributions from available data. For instance, for estimating the interspecies AF distribution, both animal and human toxicity data would be required. Since human data are not available for most chemicals, data from two animal species have been used as a surrogate. A number of NTP studies were analysed where the same compounds had been tested in both rats and mice. This resulted in an estimate of the interspecies AF distribution for these two species. A subchronic-to-chronic AF distribution was established in a similar way in another study. For intra-species variation, a distribution is less easy to estimate, and so far indirect arguments must be used in postulating a specific distribution.

16. When these distributions are applied to the reference point (which could be a NOAEL or a BMD with an associated uncertainty distribution), a distribution of the potential "safe" dose for the sensitive human can be derived. A lower percentile of that distribution may then serve as a probabilistic RfD. In this way, the level of conservatism associated with the (probabilistic) RfD may be harmonised among different risk assessments (which is currently not the case for the ADI/TDI).

17. A next step is to integrate such a probabilistic hazard characterisation with a probabilistic exposure assessment into an integrated probabilistic risk assessment. Two examples were discussed. For diethylhexylphthalate (DEHP), it was assumed that the variability in the exposure assessment is much larger than the uncertainties involved; therefore, the uncertainty can be ignored. For the hazard characterisation only uncertainties were considered. This approach results in a plot with fraction of the (sensitive) human population on the x-axis, and the probability that any individual would exceed the "no-adverse-human-effect-level" on the y-axis. In this way, both variability in exposure among individuals, and scientific uncertainties (due to lack of data) are made visible in the final risk characterisation (Bosgra 2005).

18. The second example related to acephate (an organophosphate), which may be present on fruits and vegetables. Here, a further step was taken: both variability and uncertainty were accounted for in both the exposure assessment and the hazard characterisation. The approach followed was to specify the probability that a random individual from the human population would have an exposure high enough to cause a particular health effect of a predefined (but small) magnitude, the critical effect size (CES), such as a 20% decrease in acetylcholinesterase-activity. The exposure level that results in exactly that CES in a particular person is that person's individual critical effect dose (ICED). Individuals in a population typically show variation both in their individual exposure (IEXP) and in their ICED. Both the variation in IEXP and the variation in ICED are quantified in the form of probability distributions. Assuming independence between both distributions, they are combined (by Monte Carlo) into a distribution of the individual margin of exposure (IMoE). The proportion of the IMoE distribution below unity is the probability of critical exposure

(PoCE) in the particular (sub)population. Uncertainties involved in the overall risk assessment (i.e., both regarding exposure and effect assessment) were quantified using Monte Carlo and bootstrap methods, resulting in an uncertainty distribution for the probability of critical exposure (PoCE). From these calculations plots could be derived that concisely summarised the probabilistic results, retaining the distinction between variability and uncertainty.

19. The advantage of this approach (compared to the first example) was that, for any particular exposure situation, the plot shows: the fraction of the population that would exceed their (personal) critical dose, the extent of exceedance, together with the uncertainties around it. In addition, the relative contributions from the various sources of uncertainty involved could be quantified. The latter information makes clear which uncertainties in the overall risk assessment are greatest and deserve primary attention (Van der Voet and Slob 2007).

Exploring Uncertainty Using Sensitivity Analysis

20. Probabilistic risk assessments that use a mathematical model generally assume that the model is 'correct'. In reality, uncertainty from parameters and model structure propagate through to model predictions. The minimisation of these uncertainties is central to producing a meaningful risk assessment.

21. Sensitivity analysis is a tool that can focus model corroboration, direct research and prioritise additional data collection. However, sensitivity analysis describes a host of distinct techniques, each with their own strengths and applicability to the questions faced when developing and analysing a model. Whilst the more commonly used ‘local’ methods are computationally inexpensive and provide information on model behaviour for specific parameter combinations, their results are often misinterpreted as providing general statements to the behaviour of non-linear models. The use of a model-independent, quantitative, global sensitivity measure offers insight into model behaviour that is not provided by local methods.

22. Discussion focussed on an approach to global sensitivity analysis that uses an initial screening by the Morris method to identify the model's most influential parameters, followed by application of the Extended Fourier Amplitude Sensitivity Test (FAST) (Morris 1991, Saltelli *et al.* 1997). These methods were chosen on the basis of their applicability to diverse model structures; computational cost; complexity of their application and representation of the sensitivity. A didactic example of a sensitivity analysis performed on two physiologically based pharmacokinetic (PBPK) models was analysed. Differences between the results provided by local and global techniques were considered and methodologies determined for: model reduction, parameter estimation, model corroboration, and identification of subgroups susceptible to toxic effects within a population.

23. The methods examined could drastically reduce the time and effort involved in producing population models that predict human variability. They also provide a means for focusing research on the parameters that will provide the greatest increase in confidence in the model predictions.

Framework Approaches in Risk Assessment and Weight of Evidence Considerations

24. Structured frameworks are extremely useful in promoting transparent, harmonised approaches to the risk assessment of chemicals. There has been particular activity in developing a systematic approach to determining the mode of action of the carcinogenic effects of chemicals in experimental animals and to evaluating the potential human relevance of these effects. This work led to a publication by the IPCS (Boobis et al, 2006), which was an update of an earlier publication of a mode of action framework in animals (Sonich-Mullin *et al.* 2001). The first stage of the approach is to determine whether it is possible to establish a hypothesised mode of action on the basis of the experimental data. This comprises a series of key events along the causal pathway to cancer, identified using a weight of evidence approach based on the Bradford Hill criteria. The key events are then compared first qualitatively and then quantitatively between the experimental animals and humans. Finally, a clear statement of confidence, analysis and implications is produced.

25. More recently, this work has been extended to non-cancer effects. The ultimate objective is to harmonise framework approaches to cancer and non-cancer endpoints. The process for non-cancer endpoints is very similar to that for cancer endpoints. The first step is to determine whether, on the basis of experimental data, the weight of evidence is sufficient to establish an hypothesised mode of action, using an approach based on the Bradford Hill criteria (Hill 1965). This is followed by a qualitative and then a quantitative comparison of the key events between experimental animals and humans. Finally, there should be a clear statement of the conclusions, together with the confidence, analysis and implications of the findings.

26. Such frameworks enable a more transparent evaluation of the data, identification of key data gaps and a structured presentation of information that would be of value in the further risk assessment of the compound, even if it is not possible to exclude relevance to humans. For example, there may be data on the shape of the dose-response curve, identification of thresholds or recognition of potentially susceptible sub-groups, based on genetic or life stage differences, for example.

Meta-analysis and the Combination of Epidemiological and Toxicological Evidence

27. Improving the design of individual animal studies is a key strand of the NC3Rs[e] programme, but the next stage in the decision process, reviewing and combining results from individual primary studies, also needs attention; the 3Rs need to be supplemented by a 4th R: (Systematic) Review. Systematic review and meta-analysis methods (Sutton *et al.* 2000, Egger *et al.* 2001) are widely used to summarise and combine results of clinical trials, forming the basis for evidence-based medicine[f]. They are increasingly popular in epidemiology, and in health and social policy areas, but they remain relatively rare in toxicology. The talk included some results from a recent systematic review of the use of systematic review and meta-analyses in animal experiments (Peters *et al.* 2006). Low uptake of systematic review and meta-analysis in toxicological contexts may stem partly from the perception that they conflict with selection of pivotal primary studies on grounds of study quality and relevance. In fact systematic review and meta-analysis do not require uncritical pooling of all evidence, just explicit criteria for any selectivity.

28. Systematic review and meta-analysis methods can contribute at two stages in the use of evidence from animal studies: for the review and combination of results i) of animal studies alone, and ii) of animal studies with evidence from humans. Application of two Bayesian synthesis approaches (extensions of the basic meta-analysis method) to the latter are briefly described here (Peters *et al.* 2005, DuMouchel and Groër 1989). The methods offer an approach to formalisation of the use of 'uncertainty factors' for inter-species effects. Transparency in a systematic review regarding the various assumptions made to identify, obtain and select relevant evidence of an appropriate quality allows reproducibility, and facilitates updating as new evidence becomes available. Quantitative synthesis of results from several primary studies offer greater statistical power and more precise estimates than the primary studies on which they are based, and provide a framework for investigation of sources of heterogeneity and quantitative sensitivity analyses.

[e] National Centre for the Replacement, Refinement and Reduction of Animals in Research. See http://www.nc3rs.org.uk/ (last accessed 08 January 2007).
[f] Cochrane Collaboration. See http://www.cochrane.org/ (last accessed 08 January 2007).

Committee Discussion

BMD Approach

29. The BMD approach was considered to offer benefits over the NOAEL approach, since it takes the variability in the effects seen at each dose into account. There is implicit model uncertainty since the BMD approach is merely the pragmatic application of models to dose response data. It is generally appropriate to select the most conservative BMDL, having excluded biologically implausible models. Failure to fit any of the available models suggests that there are insufficient data upon which to base a robust analysis; however, Members were concerned that data available for many of the assessments conducted by COT may be inadequate for dose-response modelling.

30. The COT had used a BMDL in establishing a TDI for perfluorooctanoic acid (PFOA)[g]. This approach was taken because the lowest NOAEL of 0.06 mg/kg bodyweight (bw) per day was for hepatotoxicity in a 90-day study, whereas a 2-year study conducted in the same strain of rat indicated a much higher NOAEL of 1.3 mg/kg bw/day. Modelling both sets of data resulted in BMDL values of 0.3 and 0.74 mg/kg bw/day, respectively, hence reducing the apparent inconsistency between the two studies. It was considered premature for the Committee to adopt the BMD as the default approach until each step of the process - its theoretical basis, implicit assumptions and practical application - are thoroughly understood. It would be inappropriate to view the BMD as a superior NOAEL. Movement from the NOAEL to the BMDL would mean risks would be expressed in terms of level of effect (BMDL) rather than level of no effect (NOAEL); therefore, risk assessments might be better communicated in terms of level of protection. In addition, the acceptable risk for the critical effect size needs to be further considered.

31. The application of the BMD approach to data from two recent COT evaluations, providing examples of a rich and poor data set, might aid the Committee's deliberations. It was also noted that the European Food Safety Authority (EFSA) is also evaluating the BMD approach. The result of this evaluation should inform Committee discussions.

Allometric Scaling

32. Allometric scaling between different animal species and humans is based on the basal metabolic rate. It may therefore be more appropriate than bodyweight scaling, for chemicals whose clearance from the body is determined by basal metabolic rate. However, many chemicals assessed by the Committee rely upon specific enzymes and protein transporters for their toxicity and/or elimination. The specificity and level of expression of these proteins can differ vastly between species and may not necessarily scale allometrically. It is not possible to predict chemicals for which

[g] http://www.food.gov.uk/multimedia/pdfs/cotstatementpfoa200610.pdf

allometric scaling is appropriate, which complicates the use of allometric scaling as the default method.

Assessing Uncertainty

33. The COT report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment emphasises the need for uncertainty to be taken into account. Expression of uncertainty is also required in the Science Checklist[h] recently adopted by scientific committees that provide advice to the Food Standards Agency. The Committee agreed that more consideration should be given to communication of uncertainty, qualitatively and/or quantitatively; perhaps adopting a formal method for recording the uncertainty in Committee statements. However, Members noted that quantification of uncertainty in an integrated risk assessment could lead to spurious precision which may be misinterpreted.

Probabilistic Approaches to Hazard Characterisation, Exposure and Risk Assessment

34. Probabilistic approaches offer some advantages in refinement of risk assessment, but may have greater requirements for data and resources. These higher tier methods could be used as required, on a case-by-case basis.

Framework Approaches to Risk Assessment

35. Framework approaches can offer greater transparency to the risk assessment process. They should be used, when appropriate, and follow the IPCS recommendations (Boobis et al, 2006).

Systematic Review and Meta Analysis

36. Guidance has been recently given to the Secretariat regarding the conduct of literature searches and reviews. This requires search terms to be included as an annex to Committee papers. The recent systematic review of fume events (TOX/2007/010, Annex 10) was cited as an example where such a review is very helpful. Bias against publishing negative results can affect the results of all review techniques, although meta analysis can make this bias more clear.

37. Formal combined analysis of epidemiological and toxicological data in a meta-analysis is appealing; however, there are a number of unresolved issues. Toxicology studies are often complex and differences in experimental protocol (such as day of dosing) may need to be taken into account during a systematic review or meta analysis. It is important that those conducting a systematic review are clear in reporting how the review has been conducted. Similarly, a common situation arises when

[h] Annexe 4 of http://www.food.gov.uk/multimedia/pdfs/fsa060207.pdf

several different sets of animal data provide conflicting NOAELs (or BMDLs). Statisticians suggest simply combining the data by meta-analysis would be unwise, and it may not be possible to provide a satisfactory explanation for differences.

38. Epidemiological data should always be interpreted in the context of available experimental data from animals, particularly when considering the plausibility of causation as an explanation for observed associations. It may be preferable to compare the results of separate reviews of human and animal data. It is important that the relative weight given to human and animal data should be clearly reported, considering sensitivity analysis where appropriate. It was suggested that meta-analysis be attempted on an example from the future COT agenda.

Overall Conclusions

39. The workshop emphasised the need to more explicitly assess and describe the uncertainty in the available data; many of the methods included in the workshop offer the opportunity to do this. The use of more transparent and reproducible methods is also important, such as framework approaches and systematic rather than narrative review.

40. Adopting new approaches should be carefully considered and only implemented if they offer a clear benefit in terms of improving the risk assessments provided by the Committee. Where possible and where appropriate, new approaches should be initially performed in parallel with existing methods, allowing for further investigation of divergent outcomes.

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