COT Report on Variation and Uncertainty in Toxicology Summary of Consultation Responses

Background

The draft Report was released for UK consultation on 10th April 2006 with a request for responses by 10th July 2006. Some responses arrived after this deadline, but where still considered. A total of 15 responses were received, 12 of which contained substantive comments. The others simply acknowledged receipt of the draft Report.

After the end of the consultation period, COT Working Group on Variation and Uncertainty in Toxicology (VUT) considered the responses via meetings and written communications with the Secretariat. Subsequently, the draft Report was amended by the Working Group to take account of many of the issues raised by respondents to the consultation. The final Report has now been adopted by the COT and published.

Summary of responses

The following organisations, committees and individuals provided comments in response to consultation:

- Advisory Committee on Pesticides (Jon Ayers, Chairman)
- Margaret Anderson, Ludlow, Shropshire
- Richard Bruce, Yarmouth, Isle of Wight
- David Coggan, MRC Epidemiology Resource Centre, Southampton General Hospital
- Crop Protection Association (Anne Buckenham, Director of Policy)
- Georgina Downs, UK Pesticides Campaign
- Michael Festing, MRC Toxicology Unit, University of Leicester
- Fund for the Replacement of Animals in Medical Experiments: FRAME (Nirmala Bhogal and Robert Combes)
- Health and Safety Laboratory's Computational Modelling Section (Anna Rowbotham and George Loizou)
- Geoff Pigott – consultant toxicologist
- Margaret Reichlin, Andover, Hants
- Douglas McGregor – consultant toxicologist, Toxicity Evaluation Consultants

Some of the responses were quite extensive, making many specific comments and suggestions for changes to the Report. Many of the comments were used as the bases for improvements to the draft Report. The major issues raised in responses to the consultation are summarised in the table below.

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Issues raised	Respondents raising the issues	How the issues are dealt with in the VUT Report
It was suggested that the Report made a too clear distinction between variation and uncertainty	David Coggan	The VUT considered it appropriate to make a clear distinction between variation and uncertainty, but added text to explain that uncertainty about the amount of variation is considered to be a source of uncertainty.
It was suggested that more discussion of "omics" methods (genomics, proteinomics, metabolomics, etc) could usefully be added.	Crop Protection Association; Michael Festing	The COT is keeping a watching brief on this issue and has published two statements so far. The use of "omics" in toxicology was considered promising, but not as yet ready for use in routine regulatory toxicology. The methods are mentioned in the Report, but it was considered inappropriate to discuss them in greater detail in this Report.
A reasoned proposal was made for the use of a battery of several fully sequenced strains of laboratory animals, possibly along with *in vitro* "omics", in place of current strains of animals used in toxicology.	Michael Festing; Advisory Committee on Pesticides	The VUT discussed the pros and cons of such an approach, and added text to the Report to reflect its views (in paragraph 4.1 and elsewhere). They considered it more representative of variation in the human population to use strains of animals with a range of genotypes (as in current testing regimes). Michael Festing's article was cited in paragraph 5.1.
It was noted that the draft Report did not cover the effect on the overall uncertainty in results of toxicology studies caused by variability associated with the design and conduct of studies. Sources of possible variability were given as examples: group size, housing density, diet and	Geoff Pigott; FRAME	Some of the points were already covered in general terms, but some rewording and additional text was introduced to cover other issues raised here.

environmental conditions.		
The need for extensive discussion of testing for endocrine modulation and developmental neurotoxicity was questioned.	Geoff Pigott; FRAME	The VUT noted that these are current areas of interest in regulatory toxicology. It considered it to be useful to use these areas as examples of areas of toxicology in which there is specific uncertainty that could be reduced by further research. The chapters on Developmental Neurotoxicity and Endocrine Modulation were retained.
It was suggested that the draft Report had a disproportionate amount of discussion of variability and uncertainty in human studies at the expense of discussion of variability and uncertainty in data from animal tests.	FRAME	The VUT considered it appropriate to discuss in some detail variability and uncertainty in both human and animal studies. No changes were made to specifically address this issue.
It was suggested that more could be said about how *in vitro* and *in silico* data could be used to inform the extrapolation of data from animal tests to human risk.	FRAME	These issues were already mentioned in the Report in the context of discussing different types of studies, both as means of reducing uncertainty and as possible sources of variability and uncertainty in toxicology. A more detailed discussion of these issues would upset the balance of the report by putting undue emphasis on the use of *in vitro* and *in silico* methods. The VUT considered the current text to give an appropriate discussion of the role of these methods in toxicology and there was no need to amend the Report in the way suggested.
It was suggested that the Report's discussion of polymorphisms of transporters and receptors should be more related to the practicalities of toxicity testing.	FRAME	The VUT considered that the discussion was appropriate for its context and did not alter the text.

It was suggested that the discussion of CYP-polymorphisms could be improved by a mention of the potential contribution of genetically engineered batteries of cell lines expressing variants of some human CYPs to improve the estimation of risk.	FRAME	The issue raised was peripheral to the remit of the VUT and it was decided that there was no need to make specific mention of such tests.
Several issues were raised relating to the possible increased susceptibility of children to chemical toxicity.	Crop Protection Association	All the issues are already covered in the Report and the VUT agreed that the Report did not need to be amended.
Several detailed points were made in relation to the susceptibility of children to toxicants and the possible need to use an addition safety factor for children.	Crop Protection Association	It was noted that the draft Report already dealt adequately with these issues and there was no need to amend the text.
It was noted that European legislation allows the use of the threshold of toxicological concern (TTC) approach for risk assessment of pesticide residues in drinking water.	Crop Protection Association	Text was added to the Report to cover this issue.
It was suggested that the text should include a discussion of use of the benchmark dose in place of the NOAEL.	Douglas McGregor	It was noted that the benchmark dose is described in Chapter 12 and the text includes a discussion of its use in place of a NOAEL. There was no need to amend the text.
Concern was expressed that relevant subjective evidence from exposed people might sometimes be overlooked.	Margaret Reichlin; Richard Bruce	It was noted that this refers to possible variability in response between different people. This was one of the reasons that the COT identified a need for a report on variability and uncertainty in toxicology. The VUT ensured that this issue was covered in the Report.

It was pointed out that uncertainty about safety has sometimes been used as a reason to keep substances on the market or as a reason not to act against environmental contaminants while proof of harm is sought.	Margaret Reichlin; Georgina Downs	The issues raised relate to risk management decisions, and as such are outside the remit of the VUT.
The current systems for post-marketing surveillance of pesticides and medicines were criticised.	Richard Bruce	This issue does not have direct relevance to the Report.
It was noted that current systems for assessing the safety of substances are designed to protect the majority of the population, but do not always guarantee the safety of at-risk sub-populations, such as babies, the elderly, pregnant women and the sick.	Georgina Downs; Richard Bruce	The various aspects of these issues as they relate to variability and uncertainty in toxicology are covered in detail at various points throughout the Report. Polymorphisms, in particular, are covered extensively in Chapters 5 & 6, and human variability is dealt with in Chapter 8. The special risks to young children, pregnant women, the elderly and the sick are deal with at paragraphs 3.21, 3.44, 4.21, 5.13 and 5.18. It is concluded in the Report that the toxicokinetics of substances are affected by age, stage of development and functional maturation of organs and systems, co-exposure to other agents and compounds (eg. nutrients), lifestyle, environmental factors and disease. For most substances, there is incomplete information on the susceptibility of at-risk sub-populations and it was recognised that there is a need for better characterisation of the uncertainties related to possible altered susceptibility arising from environmental, physiological and metabolic changes during the course of life and in older life. It was recommended that vulnerable groups of people should be identified. Research should be performed to determine whether there are specific subgroups not protected by the

		default uncertainty factors; to identify valid mechanism-based biomarkers of uptake, effect and susceptibility that would help to identify subgroups at risk; and to better characterise the hazards to older people in order to determine whether current uncertainty factors are appropriate.
It was noted that there have been suggestions that neurological or psychological diseases such as schizophrenia, autism and Parkinson's disease might be associated with environmental exposure to chemicals.	Georgina Downs; Richard Bruce	Apart from this being one of many examples of uncertainty in toxicology, this issue has little direct relevance to the Report. No amendments were made.
Concern was expressed that ingredients other than the active ingredients in formulated products rarely are tested to the same extent as the active ingredient.	Richard Bruce	In various chapters, the Report covers this issue in general terms by explaining that the type and amount of toxicological testing required can be determined by a variety of considerations, including cost, the amount of human exposure, the presence of structural alerts in a chemical structure and history of safe use. Limited testing maximises uncertainty about the safety of a chemical. To go into this issue in more detail would be to stray away from the remit of the VUT.
It was pointed out that exposure assessment is a major source of uncertainty and variability and that this can be a major contributor to the reliability of the risk assessment.	Richard Bruce	The Report acknowledges this, and makes clear exposure assessment was outside the remit of the VUT. A reference was made to a recent document from EFSA that dealt with uncertainty and variability in exposure assessments.
It was suggested that a negative result for delayed polyneuropathy in the hen test is not a reliable indicator that a substance will not produce organophosphate-induced delayed	Richard Bruce	The VUT did not agree with the claim made here and considered the hen test to be the best method available to show that a substance is unlikely to cause OPIDP in humans. The hen is more sensitive to this effect than humans, so a negative result in hens gives

polyneuropathy (OPIDP) in exposed humans and that some commonly used OPs can cause diagnosed OPIDP in human. It was noted that several successful court actions by sufferers have highlighted this issue.		assurance of the safety of humans. The Report also discusses the importance of post-marketing surveillance of approved substances (eg. pesticides) for identifying the rare instances when adverse effects were not picked up by the routine toxicological testing. No change to the text was needed.
Concern was expressed that interaction or synergism between different chemicals could result in unanticipated adverse effects if chemicals are assessed one-by-one. It was claimed that this issue was dealt with only in relation to endocrine modulators, whereas it is a more general problem. It was suggested that there is a need for more research into interactions between substances administered at the same time or within a short-time of each-other.	Georgina Downs; Richard Bruce; FRAME	This issue was in fact dealt with at several points throughout the Report (eg. Paragraph 5.26 deals with mixtures of substances), as well as in the endocrine modulators chapter (Chapter 10). One of the recommendations of the Report is for further work into the effects of mixtures of chemicals. The COT has also considered mixtures as part of other discussions, both from the generic perspective and in evaluating specific groups of chemicals.
The ACP agreed with the conclusion that there ass a need for a pre-planned robust mechanism for assessing the results of studies that seemingly give contradictory results. However the ACP considered that it was rather unclear from the Report what was intended. The ACP went on to note that contradictory results often present real difficulties in interpretation of a data package.	Advisory Committee on Pesticides	The wording of the relevant conclusion was expanded to take account of the comments and corresponding text was added to the body of the Report.