COMMITTEES ON TOXICITY, MUTAGENICITY AND CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

JOINT STATEMENT ON A SYMPOSIUM HELD BY THE THREE COMMITTEES ON THE USE OF GENOMICS AND PROTEOMICS IN TOXICOLOGY

Introduction

1. Sir Robert May’s “Review of Risk Procedures used by the Government’s Advisory Committees dealing with Food Safety” recommended greater collaboration between expert committees covering overlapping areas. A joint symposium to discuss the use of genomics and proteomics in toxicology was considered a suitable opportunity for collaboration between the three committees (COT, COM and COC). The meeting, held on 8 October 2001, included members of various other expert committees, delegates from government departments and invited speakers and was also open to interested parties.

2. The topic was chosen in response to an increasing need to consider the role that novel technologies such as proteomics (or protein profiling) and genomics (or more accurately in the context of this workshop, transcript profiling) may play in toxicological risk assessment. This area has been given added impetus since the publication of the human genome sequence and it was considered important to consider if and how data obtained using such techniques may be incorporated into regulatory processes. The objectives of the meeting were thus defined as:

   • To provide advice to government departments and regulatory agencies on use of genomics and proteomics in toxicological risk assessment

   • To facilitate closer working and greater collaboration between the COT, COC and COM.

3. The symposium was divided into three sessions: an introduction, a detailed discussion of the subject areas and a final summary and conclusions session. Three working groups considered the issues of genomics,
proteomics and the use of genomics and proteomics in risk assessment, respectively. Each group had a presentation from an expert in the field followed by a targeted discussion, facilitated by a member of one of the committees (COT, COC or COM).

**Genomics**

4. The working group concluded that data from toxicogenomic studies could not be used in isolation for risk assessment purposes but that such data could be considered as part of a ‘weight of evidence’ approach. Gene expression studies could not, at present, be used to define NOELs and NOAELs. It was considered that there was a need to correlate changes in gene expression to corresponding conventional toxicology data and histopathology. It was also agreed that it was essential to distinguish between changes in gene expression representing background variation, adaptive pharmacological effects and those that represent adverse effects.

5. It was agreed that genomics data might be useful for limited screening for toxicological mechanisms and endpoints such as hormonally mediated carcinogenesis, mutation in error-prone DNA synthesis caused by genotoxic carcinogens and adverse effects on reproduction other than teratogenicity. It may also be useful for investigating organ specific effects of chemicals earlier in their pathogenesis than the appearance of frank pathological lesions as detected by light microscopy. However, further research was required before the technology could be applied to other areas. For example, in neurotoxicology it is difficult to correlate structural targets in the nervous system to the neurotoxicant’s site of action particularly as validation using conventional toxicological methods is limited. At present, genomics is also unlikely to be of use in teratology studies due to the rapid rate of change in the developing organism. It was proposed that transcript profiling might be valuable also for evaluation of adverse effects resulting from the interaction of chemicals with the immune system. Clearly there are important opportunities for the application of toxicogenomics, but also some limitations. Presently it is likely that the main benefits will be in characterisation of mechanisms of actions and the identification of new markers for hazard identification.

**Proteomics**

6. It was concluded that proteomics could not be used for regulatory purposes at this stage. However, the technology might be useful for screening candidate compounds where there is some knowledge of the mechanisms of toxicity. Proteomics may also be useful in identifying novel mechanisms. Data from proteomic studies can only be used for refining NOAELs in defined circumstances where the pattern of protein changes under investigation can be causally related to the toxic mechanism and observed pathology, and the study includes dose-response data. The Committees noted that a collaborative initiative to provide validation data for proteomic studies was crucial as problems with reproducibility between studies have often compromised their potential for use in risk assessment. Similarly, the group
agreed that there is an urgent need to develop databases to aid protein identification.

7. The potential for using proteomics in non-invasive human biomarker studies was acknowledged. However, the reproducibility and dose response of any potential proteomic biomarkers would need to be established and compared to existing methods with regard to specificity and sensitivity before they could be used for risk assessment.

Risk Assessment

8. It was agreed that although genomics and proteomics show great potential for risk assessment, caution should be applied when drawing conclusions from data derived from such technologies. These may be difficult to interpret and input from bioinformatics specialists and statisticians with suitable expertise and experience is considered essential. Genomics and proteomics may be used to identify possible mechanisms of action, biomarkers of exposure and predictors of effect, but their use in these areas is dependent upon knowledge of gene function and the relationships between gene expression and biological effects. Further research into the natural background variation in gene expression is considered essential to aid in interpreting the data from such studies.

9. The use of proteomics and genomics in risk assessment was not considered likely to lead to a reduction in the use of animals in toxicology studies in the short-term. However, the use of genomics and proteomics should lead to more appropriate use of both in vivo and in vitro model systems where the extrapolation to man can be based on a fundamental understanding of differences in gene and protein expression between the systems. Future development of these technologies may provide sufficient data to enable toxicological studies to be more focused.

Overall conclusions

10. We recognise the future potential of proteomics and genomics in toxicological risk assessment.

11. We note that these techniques may serve as adjuncts to conventional toxicology studies, particularly where proteins under investigation are known to be causally related to the toxicity.

12. However, we consider that research and validation is required before these techniques can be considered for routine use in regulatory toxicological risk assessment. In particular, there is a need for more research leading to development of genomic/proteomic databases, methods of bioinformatic and statistical analysis of data and pattern recognition and for information on the normal range of gene expression.
Sir Robert May was the Government’s Chief Scientific Advisor from 1995 to 2000 when he was succeeded by Professor David King.

Office of Science and Technology, July 2000; http://www2.ost.gov.uk/policy/issues/food_safety/index.htm

International Human Genome Sequencing Consortium (2001) Initial sequencing and analysis of the human genome; Nature 409, 860-921