Descriptive vs. Quantitative Risk Assessment of Genotoxic Carcinogens

Date: 2nd April 2009

Venue: Skipton House, London

WORKSHOP REPORT

BACKGROUND

UK Government departments/agencies when assessing the risks of genotoxic carcinogens have, in the past, largely applied the qualitative approach recommended in the Committee on Carcinogenicity (COC) guidelines. However, through growing EU regulatory activities, UK Government increasingly needs to consider the outcomes of quantitative approaches applied by other member states.

OBJECTIVES

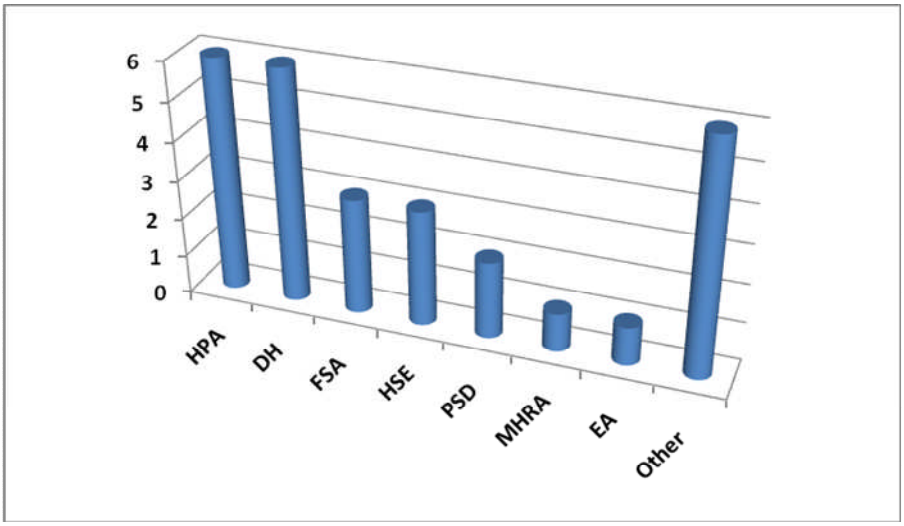
The overall aim of the workshop was to initiate a debate on the benefits and disadvantages of the application of descriptive and quantitative methodologies to the assessment of risk of genotoxic carcinogens.

A number of objectives were identified for the workshop:

- To ascertain current utilisation of descriptive and quantitative approaches in the risk assessment of genotoxic carcinogens in the UK, Europe and USA;
- To explore the benefits and disadvantages of the two methodological approaches;
- To consider whether in recent years there have been significant developments in the quantitative approaches;
- To determine the need for further activity, including a possible referral of the issue to the COC for thorough analysis and debate.

DELEGATES

A total of 28 participants attended the workshop, including delegates from a number of government departments, members of the COC and IGHRC Secretariat (designated 'other') as follows:



HPA – Health Protection Agency; DH – Department of Health; FSA – Food Standards Agency; HSE – Health and Safety Executive; PSD –Pesticides Safety Directorate; MHRA – Medicines and Health Care products Regulatory Agency; EA – Environment Agency

INTENDED OUTCOMES

Through presentations from invited UK and other EU experts followed by discussion on the application of descriptive and quantitative risk assessment approaches to genotoxic carcinogens, the workshop outcomes were intended to be:

- to raise awareness of the extent/limitations of risk assessment approaches to genotoxic carcinogens;
- to highlight any further need for a full debate and any follow-up activity of the scientific and practical aspects of these approaches.

WELCOME AND INTRODUCTION TO THE IGHRC

Professor Len Levy: Chair IGHRC Executive Committee

Professor Levy welcomed all participants to the workshop and thanked speakers for agreeing to take part. A brief introduction to the work of IGHRC was given, followed by a brief outline of the workshop programme and potential discussion points.

This presentation is available at http://ieh.cranfield.ac.uk/ighrc/Des%20vs%20Quantitative.htm

COC APPROACH TO RISK ASSESSMENT OF GENOTOXIC CARCINOGENS

Professor David Phillips: Chair COC (Institute of Cancer Research; ICR)

During this presentation, David Phillips outlined the COC (UK) approach to the assessment of genotoxic carcinogens. A four -stage evaluation strategy was presented which included hazard identification, hazard characterisation, exposure assessment and risk characterisation. Each of the 4 stages was further described in detail.

The COC approach was outlined as follows. For non-genotoxic carcinogens COC may apply a threshold approach (no observed adverse effect level (NOAEL) + uncertainty factors). However, genotoxic carcinogens are considered as non-threshold; the use of quantitative extrapolation techniques is considered as being too imprecise. The ALARP (as low as reasonably practicable) is therefore adopted with the MOE (margin of exposure) approach being considered for risk communication/prioritisation purposes.

This presentation is available at http://ieh.cranfield.ac.uk/ighrc/Des%20vs%20Quantitative.htm

UK APPROACH TO ASSESSMENT OF GENOTOXIC CARCINOGENS IN THE OCCUPATIONAL SETTING

Dr Susy Brescia (HSE)

Dr Susy Brescia described the current approach taken in the UK to the assessment of genotoxic carcinogens when dealing with chemicals manufactured and used in the workplace. Although chemicals with mutagenic properties are generally banned for use by the general public without requiring a risk assessment, the same chemicals are not banned from use in an occupational setting. For the industrial/professional use of chemicals with mutagenic property the societal position has been to seek to manage the risks.

An operational description/definition of a genotoxic carcinogen was provided and a distinction between genotoxic carcinogens, for which a threshold can be identified, and those for which a threshold cannot be identified was made. The approach (ALARP) adopted in the UK to the risk management of those genotoxic carcinogens for which a threshold cannot be identified was described, with particular emphasis on its implementation in an occupational setting. Dr Brescia described the benefits and disadvantages of the approach and raised a point for discussion on whether or not, with the mechanistic information now available on genotoxicity and carcinogenicity of many compounds, it was time to 'push the boundaries' with regards to moving away from current methods.

This presentation is available at http://ieh.cranfield.ac.uk/ighrc/Des%20vs%20Quantitative.htm

DEALING WITH GENOTOXIC CARCINOGENS: THE VIEWS OF AN EU-RECOGNISED EXPERT
Professor Hermann Bolt

The strategy of the EU SCOEL (Scientific Committee on Occupational Exposure Limits) to setting occupational exposure limits (OELs) for genotoxic carcinogens was outlined by Professor Bolt. Indirect genotoxic mechanisms were described and SCOEL criteria for defining genotoxic carcinogens as having threshold or non-threshold effects presented. Examples of different genotoxic carcinogens categorisations were given.

In summary, the approach of SCOEL is to define health-based OELs for carcinogens with an established threshold effect; where OELs cannot be defined, a quantitative risk assessment is carried out; where data are insufficient for quantitative risk assessment, strategies to minimise risks are recommended (*Hermann M. Bolt, Alicia Huici-Montagud (2008) Strategy of the scientific committee on occupational exposure limits (SCOEL) in the derivation of occupational exposure limits for carcinogens and mutagens. Arch Toxicol 82:61–64).*

This presentation is available at http://ieh.cranfield.ac.uk/ighrc/Des%20vs%20Quantitative.htm

EFSA MOE APPROACH
Dr Sue Barlow

Dr Barlow presented the Margin of Exposure (MoE) approach adopted by the EFSA (European Food Safety Authority). The advantages and disadvantages of several available approaches were described, with emphasis on the MoE approach.

The process of deriving MoEs using the Bench Mark Dose (BMD) approach was detailed and its practical application by JECFA (Joint FAO/WHO Expert Committee on Food Additives) and EFSA (European Food Safety Authority) in the evaluation of naturally-occurring and man-made genotoxic carcinogens in food was described. In summary, the advantages and limitations of the MoE approach were given.

This presentation is available at http://ieh.cranfield.ac.uk/ighrc/Des%20vs%20Quantitative.htm

DUTCH APPROACH TO RISK ASSESSMENT OF GENOTOXIC CARCINOGENS
Dr Dinant Kroese

The Dutch approach to the risk assessment and limit setting for genotoxic carcinogens was presented by Dr Kroese (additional information on the Dutch Approach has been provided by Dr Kroese and is detailed in Annex 1). OELs for non-threshold genotoxic carcinogens are established in a 3 step-process involving, the quantitative assessment of carcinogenic risks by linear extrapolation, the recommendation of an appropriate air concentration corresponding to a reference value of excess cancer risk considered acceptable/tolerable and an assessment of the feasibility of the reference value. Individual stages were described in detail and examples of genotoxic (both threshold and non-threshold mechanisms) and non-genotoxic carcinogens were outlined. The use of linear extrapolation was identified as a key feature of the Dutch approach.

This presentation is available at http://ieh.cranfield.ac.uk/ighrc/Des%20vs%20Quantitative.htm

US APPROACH TO RISK ASSESSMENT OF GENOTOXIC CARCINOGENS
Dr David Lovell

Dr Lovell described the USA approach to data modelling with respect to the assessment of risks of genotoxic carcinogens. A 4 step risk assessment process was described including hazard identification, dose-response assessment, exposure assessment and risk characterisation. Each of these stages was described more fully.

Dr Lovell indicated that the USEPA (United States Environmental Protection Agency) is moving away from the (mathematically) modelled extrapolation of experimental data to the simple linear extrapolation from a point of departure (POD). The benchmark dose approach was additionally described as a tool to identify the POD and comparisons between outputs from different models discussed.

This presentation is available at http://ieh.cranfield.ac.uk/ighrc/Des%20vs%20Quantitative.htm

DISCUSSION SESSION
Chair Professor Len Levy

The following points were suggested for discussion:

What are the current approaches adopted by UK government departments and agencies?
How does this compare to the risk assessment methodologies used across Europe/internationally?
What guidance has been produced?
Do the descriptive and quantitative approaches have particular use scenarios?
Does current guidance/opinion require further evaluation or summary?

Diane Benford (FSA) opened the discussion by stating that she believed the MoE approach was the one to take for carcinogens with a non-threshold mechanism as most of Europe would be happy to endorse this. Dr Benford added that the issue of a threshold/no threshold for a genotoxic carcinogen/mutagen came under COM rather than COC and those discussions had already begun. If there is sufficient evidence to assume a threshold mechanism then the MoE approach is not needed, eg. EFSA recently set a TWI for ochratoxin A. Alan Boobis (Imperial College London) commented that there was a difference in the consequence of concluding a linear-dose-response relationship for a genotoxic carcinogen between Europe and the US, and that the downstream implications for this were very different in each country.

Robin Fielder (HPA) endorsed the opinion of Dr Benford, adding that risk assessment of genotoxic carcinogens was always likely to be done on a case-by-case basis and that it could not be generalised. Len Levy (IGHRC) questioned that even with a case-by-case basis there would still need to be a discrete number of 'general' approaches and that it was not practical to have an infinite number. David Phillips (ICR/COC) responded that the default position must be one of 'no threshold' as we do not know what dose level is associated with increased risk above background. He stated that understanding the mechanism involved was vital and this had to be on a case-by case basis.

Robin Fielder informed participants that both COC and COM keep under review their positions/guidelines. Alan Boobis confirmed that at present, not enough information on the mechanism of action of genotoxic carcinogens was available and until that position changed it would be difficult to move away from the default.

Frances Pollitt (HPA/COC) suggested that rather than changing completely the way we carry out risk assessment of genotoxic carcinogens in the UK, we should look at which elements of the current practice can be improved.

Len Levy asked participants how defensible they thought the values produced by each method are. David Lovell (University of Surrey) replied that the US approach produces a range rather than a worst case scenario, which takes into account uncertainty. Although this may take away some of the precision, it may be more risk based. Robin Fielder added that if a quantitative risk assessment of genotoxic carcinogens was adopted, then it would be needed to set an 'acceptable risk level' and this should be a decision for society, not scientists.

Len Levy further asked participants for their views on whether they thought the UK approach to be too pragmatic and not scientific enough. Dinant Kroese (TNO) commented that from a scientific standpoint, the linear extrapolation calculations they carried out are not scientifically based. However, he added that the approach was transparent and very conservative.

Alan Boobis commented that COC would like to, where possible, use probabilistic approaches but that this was a big step and benefits were unclear. Robin Fielder stated that better descriptions of what is the best starting point or POD to use are needed and would look to COC for that. Sue Barlow added that MoE and linear-dose extrapolation approaches assume that potency is important. However, the issue as stated by David Phillips is that potency ranking at low doses may not be the same as at higher doses; this could cause over conservative values to be generated. David Phillips replied that biomarkers eg DNA adducts have been shown to have linear dose-response relationships which may allow estimates at lower levels. However, Diane Benford highlighted that adducts would only be reflective of recent exposure although agreed that they could prove useful for cross-species extrapolations.

Len Levy put forward the question 'was clarification needed at this point'? David Phillips replied that updated advice on MoE may be appropriate as this approach is a definite move forward. Alan Boobis asked whether COC would recommend one approach if data were available that showed it to be superior to others. Sue Barlow commented that the weight of evidence approach used by COC was a good platform to base advice on as it could include consideration of several ways of evaluating the risks.

In a closing question, Len Levy asked participants if they were content with the approach being taken at present. Mark Hosford (EA) asked whether the margin of exposure considered to be of low concern would/should be different if techniques such as PBPK modelling had been used that provided additional confidence in the assessment. Alan Boobis replied that the MoE BMDL approach already allows for use of PBPK modelling, but he acknowledged that there is no formal consideration of whether and how this should affect the margin of exposure considered to be of low concern. He added that this was perhaps something that could be looked into. Frances Pollitt added that at present there had been no formal statement regarding the MoE approach as it is still developing, however, perhaps the COC should consider doing this at some stage.

WORKSHOP OUTCOMES (CHAIRMAN'S THOUGHTS)

The consensus opinion from the Workshop Participants was that at the present time, there was no immediate need to ask COC to re-address the issues surrounding risk assessment of genotoxic carcinogens. There was a good understanding of the uses of quantitative approaches and participants from HSA and EA confirmed that they may sometimes use QRA estimates from human cancer data; however, it was considered that the remaining uncertainties associated with such mathematical methods may preclude their use as a formal approach. The current approach of the COC is flexible, because, although a default position of a qualitative assessment aided by the MoE methodology for prioritisation/communication purposes is advocated, if, on a case-by-case basis, there is evidence (mechanistic, biomarkers, human data, PBPK, etc) to suggest that a different approach is more appropriate, this should be adopted. Clearly, the methodology used for the risk assessment of genotoxic chemicals would be kept under active consideration and re-visited when new methods warranted such a review.

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PROGRAMME OUTLINE

1030	COC Meeting
1230	*Lunch*
1310	**Welcome and Introduction to the IGHRC** *Speaker: EC Chair/IGHRC Secretariat*
1315	**COC Approach to Risk Assessment of Genotoxic Carcinogens** *Speaker: COC Chair*
1335	**UK Approach to Risk Assessment of Genotoxic Carcinogens in the occupational setting** *Speaker: Dr Susy Brescia*
1355	**Dealing with Genotoxic Carcinogens: the views of an EU-recognised expert** *Speaker: Prof Hermann Bolt*
1415	**EFSA MoE Approach** *Speaker: Dr Sue Barlow*
1435	**Dutch Approach to Risk Assessment of Genotoxic Carcinogens** *Speaker: Dr Dinant Kroese*
1455	**US Approach to Risk Assessment of Genotoxic Carcinogens** *Speaker: Dr David Lovell*
1515	*Tea/Coffee*
1530	**Discussion Session – the benefits and disadvantages of the two approaches**: What are the current approaches adopted by UK government departments and agencies? How does this compare to the risk assessment methodologies used across Europe/internationally? What guidance has been produced? Do the descriptive and quantitative approaches have particular use scenarios? Does current guidance/opinion require further evaluation or summary? Chair: Prof Len Levy
1615	**Consolidation Discussion – Next Steps**
1630	**Close**

List of Participants

Name	
Lola Akintoye HSE	Robie Kamanyire HPA
Sue Barlow Independent Consultant	Dinant Kroese TNO
Jon Battershill HPA	David Lovell COC
Diane Benford FSA	Brian Miller COC
Hermann Bolt IFADO	Khandu Mistry DH
Alan Boobis COC	Mary Morrey HPA
Susy Brescia HSE	Karen O'Leary DH Toxicology Unit (Imperial College)
Asam van der Burght TNO	Ken Okona-Mensah DH Toxicology Unit (Imperial College)
Karin Burnett DH Toxicology Unit (Imperial College)	David Phillips Institute of Cancer Research (COC)
Sarah Bull HPA	Sohel Saikat HPA
Helen Ferguson HSE	Scott Samuels PSD
Robin Fielder HPA	Alison Searl IOM
Halina Garavini DH Toxicology Unit (Imperial College)	Dick Shillaker PSD
David Gott FSA	Lesley Stanley FSA
Douglas Gray HSE	Henry Stemplewski MHRA
Lesley Hetherington HPA	Eirian Thomas HPA

Name	
Mark Hosford EA	

ANNEX 1

SOME ADDITIONAL BACKGROUND INFORMATION ON THE DUTCH APPROACH (DINANT KROESE)

The Dutch risk-based system including 'acceptable' and 'maximal' risk levels at the workplace was politically agreed as early as in 1993. In 1990 a representative of the Ministry of Social Affairs and Employment suggested in the Commission GSW (Limit values of Substances at the Workplace of the Labour Council, and since 1993 of the Social and Economic Council) the possible use of risk levels for establishing limit values for carcinogenic substances without a discernable effect threshold. Initially concerns of employee representatives to take a certain health risk on the one hand, and fear of employer representatives to be confronted with undesired economic consequences (ban or unworkable strict measures) on the other hand, led to strong debates. Phrasing of a number of collective principles, of which the target risk level is only one element, finally led to an agreement:

- The use of carcinogenic substances with their associated risks and serious effects needs to be discontinued, as every exposure to these substances is associated with a risk;
- Due to absence of preferable alternatives discontinuation of a carcinogenic substance is not always possible;
- In case continuation of a carcinogenic substance is unavoidable, exposure should be kept to a minimum, i.e. exposure levels should be as low as technically achievable.
- The continued use of a carcinogenic substance should be on societal (necessity), and technical (no alternative) grounds;
- A limit value for a carcinogenic substance is not a standard that provides absolute safety; i.e. such a value should be considered an upper exposure limit only;
- In advance target levels of risk need to be established, irrespective of the chemical of concern.

Next, the discussion centred around what would be appropriate risk levels. The GSW examined risk levels applied in other areas, e.g. number of casualties due to occupational radiation (5 per 10.000 a year) or the probability of a fatal accident in 'secured' industry (1 per 10.000 a year). Also an appropriate discussion on explicit risk levels in the Dutch Parliament, as part of a National Environmental Policy Program from 1989, was taken into consideration here. In this Program a maximal acceptable risk of cancer from (non-radioactive) substances, radiation or calamity is set at 1 per 100.000 a year (for all causes) to 1 per 1.000.000 a year (for a single cause). The so-called unconcerned, i.e. acceptable risk level was established at a 100-fold lower level.

The GSW advised unanimously, taking a person's life expectancy of 76 years, an exposure period of 40 years (8 hours a day, 40 hours a week), to strife after an extra risk of 1 per 10^6 per exposure year ('target risk level'), and to not accept an extra risk level of above 1 per 10^4 per

year (‘prohibitive risk level’). Both risk levels should be considered when establishing limit values. In 1993 the Minister accepted this proposed procedure on risk levels, stating that societal and technical aspects be assessed on a case by case basis when accepting higher or lower risk levels.

As subcommittee of the Dutch Health Council DECOS establishes exposure limits for carcinogenic substances representing 4.10^{-3}, and 3.10^{-5} cancer risk levels. These derivations are published, and since 1999 available at the Health Council’s website (www.gr.nl). Subsequently, the GSW subcommittee of the Social and Economic Council asks relevant branch organisations for their input on the technical feasibility of these exposure levels (in principle excluding personal protection equipment), as presented during the workshop.

Since its introduction in 1993 about half of the carcinogenic substances whose limit values were established legally, have occupational exposure limits(OEL) at the target risk level of 10^{-6} per year, a quarter of these substances have exposure limits at the prohibitive risk level of 10^{-4} per year, and the rest are in between. The discussions in the GSW were not always without frictions, especially when it concerned substances with great economic value. Nonetheless, the final decisions were taken unanimously.

The GSW holds the view that an enterprise will comply with legal obligations in a way that OELs have to be actively reduced to as low as possible, i.e. to what is to be rightly expected, as long as the target risk level has not been achieved. In principle, OELs representing a higher than target risk will be evaluated by the subcommittee every four years, with the aim of determining whether it is feasible to lower the limit further, with the aim of ultimately reaching the target level.