Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Preface

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluates chemicals for their carcinogenic potential in humans at the request of UK Government Departments and Agencies. The membership of the Committee, agendas and minutes of meetings, and statements are all published on the internet (http://www.iacoc.org.uk/).

During 2010, the Committee again considered a varied range of items. For example, advice was provided to the Health and Safety Executive on the carcinogenicity of the pesticide dichlorvos, and we heard an interesting presentation of work on carbon nanotubes, which is of relevance to assessing their carcinogenicity. We also began a review of the way in which our guidance on the risk assessment of carcinogens is presented and this topic is likely to occupy much of the Committee's time over the next two years. I am grateful to the members of the Committee for their input on these and the other topics considered and to the secretariat for the continued provision of high quality papers.

During the year, we were informed by the Departmental of Health that, by March 2012, the COC will no longer be an advisory Non-Departmental Public Body reporting jointly to the Chief Medical Officer and the Chairman of the Food Standards Agency but would be reconstituted by the Department of Health as a Departmental Expert Committee reporting through Departmental officials. I have been assured that the Committee will retain its independence and, indeed, it is essential that this continues to be the case.

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COC evaluations

Carcinogenicity of mixtures

3.1 In 2010, the COC concluded its consideration of the carcinogenicity of mixtures. "Mixtures" was defined as combined exposure to more than one carcinogen, or to a carcinogen and other chemical(s) with potentially modifying effects, either simultaneously or at different times. The purpose of the review was to examine the data in the scientific literature on this topic, with a view to providing advice on the potential carcinogenic action of these combined exposures and on methods for testing and assessment of such effects.

3.2 This proved to be a large and difficult topic with a lack of experimental data from which to draw conclusions. The Committee concluded that it is not possible for the risk assessment process to account for the combined action of every possible mixture of carcinogens at all possible levels of exposures over all possible time frames. Nevertheless, Members considered that some general principles could be stated as follows:

(i) Mixtures of chemicals which act via the same Mode of Action (MOA) and which do not react chemically with one another, such as polychlorinated dibenzo-*p*-dioxins, can be assessed using the concept of dose additivity and relative potency factors/toxic equivalency factors.

(ii) Although there may be a substantial margin between exposure to a carcinogen and either its no observed adverse effect level (in the case of a non genotoxic carcinogen) or another point of departure (in the case of a genotoxic carcinogen), it is possible that simultaneous exposure to two carcinogens which have the same MOA may result in a lower margin of exposure. Risk assessors should be alert to this possibility when assessing a chemical which commonly occurs together with one or more other chemicals which have the potential to cause cancer.

(iii) There are several stages in the carcinogenic process at which carcinogens might interact, for example: ADME processes, DNA adduction, mutagenicity, early preneoplastic changes, proliferation, apoptosis and neoplastic transformation. MOA analysis may be of value here, in determining critical steps at which interaction might be anticipated. Potential interactions in genotoxic MOAs have been addressed in a statement by the COM.

(iv) It is postulated that otherwise non-carcinogenic chemicals, such as anti-apoptotic chemicals or chemicals which interfere with cell cycle

regulation, which alter ADME processes or which increase permeability of the skin or oral mucosa, might have the potential to interact synergistically with known carcinogens.

(v) The assessment of potential interactions in the context of carcinogenicity is complex due to the multistage nature of the process. However, we do not advocate standard carcinogenicity studies on mixtures of chemicals except in exceptional circumstances. Such studies would be costly and would require ethical consideration in view of the high number of animals required.

(vi) *In vitro* studies of interactions should be hypothesis driven, attempt to characterize the dose-response and use models relevant to *in vivo* carcinogenicity. These studies should adhere to the criteria laid out in Borgert et al (2001). Models used to evaluate the synergistic interactions between PAHs and between HCAs were, in general, complex and may not truly reflect the situation for carcinogenesis. Thus extrapolation of results for risk assessment in humans is difficult.

(vii) Overall*, in vitro* studies can be used to confirm molecular targets or provide insight into MOA identification but are not of value for the evaluation of relative potencies of chemicals or interactions at environmentally relevant exposure levels.

(viii) In terms of the risk assessment of potential interactive effects of carcinogens, exposure to a non-genotoxic carcinogen at or below the no-effect level for the critical effect contributing to the interaction is unlikely to result in an interaction with a chemical which has a different MOA. In the case of genotoxic carcinogens, in principle, effects could occur at any level of exposure which could lead to interaction. This supports the view that exposure to genotoxic carcinogens should be as low as reasonably practicable.

3.3 The COC statement can be found at http://www.iacoc.org.uk/statements/index.htm#l

Horizon scanning

3.4 The COC undertakes “horizon scanning” exercises at regular intervals to identify new and emerging issues which have the potential to impact on public health. A number of topics were identified by the secretariat for consideration by the Committee at the 2010 exercise. From these and Committee members’

own proposals, the COC decided that the following items should be taken forward:

- The role of epigenetics in cancer
- New developments in the Mode of Action framework
- Alternative test strategies to conducting a 2-year rat bioassay
- COC/COM joint meeting on thresholds of genotoxicity
- Endogenous DNA adducts
- The cancer risk of exposure to environmental tobacco smoke in childhood
- Dose-response modelling in epidemiology studies
- The use of Zebrafish in mechanistic studies
- Common strain specific tumour types

3.5 The Committee confirmed that it wished to discuss the output of the workshop held by the International Life Sciences Institute Health and Environmental Sciences Institute on Intermittent/Short-Term Exposure to Carcinogens held in December 2009 when the final report was available and would then decide whether to pursue this topic further.

3.6 Also, the Committee decided that it should consider updating existing COC statements on specific topics if new data had become available, as resources permit.

Ongoing topics

Interaction between genotype and chemicals in the environment on the induction of cancer in risk assessment

3.7 The COC has considered previously the question of whether the genetic code for individuals (genotype) is important in determining the risk of cancer from exposure to chemicals. The Committee concluded in a 2002 statement that the data then available provided no evidence of a consistent or strong interaction between the genotype of an individual and chemical induced cancer. However, it could not discount the possibility that important interactions might be discovered in the future. It added that it was important to keep this subject under review, particularly in the light of developments expected from the Environmental Genome Project and other intiatives.

3.8 At its July meeting, the COC considered a scoping paper which reported ongoing activity in the area of genomics, environmental exposure assessment and gene-environment interaction (GEI). It included details of the relevant genomic projects and noted that, since establishment of the Human Genome Epidemiology Network (HuGEnet), 25 reviews/meta-analyses have been

published which discuss the association of particular gene variants and cancer, including data on interactions among genes and environmental exposures. The paper also discussed the advent of Genome-Wide Association Studies (GWAS). These are non-hypothesis driven studies that examine genetic variation across a given genome and relate these variants to disease. It was suggested these studies could be discussed separately from other GEI studies, where specific genetic changes are examined and a priori hypotheses should be tested. The Committee decided that, while it may be inappropriate for it to make recommendations on the conduct of GWAS studies, it should have an opinion on their interpretation, in order to provide advice to Government departments and agencies on how to evaluate these studies as part of a weight of evidence.

3.9 Since the topic is broad, Members decided that further discussions should focus on determining to what extent concerns expressed in the previous COC statement have been resolved. It was agreed that the next step should be to compare, for a specific endpoint, GWAS studies and good quality studies investigating specific GEIs. As there are several studies of both types on the bladder, this was selected as the endpoint.

3.10 It was also proposed that other areas for further review might include the metrics used to assess exposure; studies assessing known rodent genetic variants that are similar to humans; and any HuGENet reviews that are within the Committee's terms of reference, paying particular attention to those where there is robust exposure information.

The carcinogenicity of carbon nanotubes

3.11 Carbon nanotubes (CNT) are rolled up sheets of carbon atoms only one-atom thick which are densely packed in a honeycomb crystal lattice. They are extremely strong, biopersistent materials which have good thermal and electrical conductivity. The COC considered an overview of nanomaterial toxicology in 2005 and discussed whether, because of their essentially fibrous structure, they might have carcinogenic potential analogous to asbestos. Subsequently, one study had provided evidence that CNT may cause asbestos like pathology when injected into the abdominal cavity of mice. However, the COC had noted that there was some debate about the validity of models used in such studies and had asked to hear a presentation on the subject. At the July meeting, the COT heard a presentation from Professor Ken Donaldson of Edinburgh University on his work on CNT.

3.12 Professor Donaldson initially discussed the potential mechanisms of asbestos carcinogenicity. He went on to describe his work on long nanotubes, which employed direct injection into the pleural cavity as this was considered a more

physiologically relevant route of exposure than injection into the abdominal cavity.

3.13 Following the presentation, the Committee discussed a number of issues with Professor Donaldson including the risk assessment of nanomaterials. It was noted that, at present, they are assessed by existing standard risk assessment methods in Europe. Nanotubes may form part of a variety of products, such as sports racquets, bike frames, display screens and may be used to strengthen cloth. There should be limited potential for exposure during normal use of many of these products, but it is possible.

3.14 The Committee discussed how best to take this issue forward but decided that a thorough review of the available literature on nanotube carcinogenicity might be unfeasibly large. Instead, the Committee will review the relatively small number of papers reporting bioassays.

Dichlorvos

3.15 Dichlorvos (2,2-dichlorovinyl dimethyl phosphate) is an insecticide acting by acetylcholinesterase inhibition. The genotoxicity and carcinogenicity of dichlorvos were evaluated by the COM, with coopted COC members, in 2002. Since then, evaluations of dichlorvos have been performed by the US Environmental Protection Agency (EPA) and the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR) of the European Food Safety Authority (EFSA) and there are some differences between the three groups in the conclusions on carcinogenicity.

3.16 At the November meeting, the Health and Safety Executive (HSE) sought the view of the COC as to whether a threshold could be assumed for the carcinogenicity of dichlorvos. The advice was to be used in formulating a position for the ongoing EU discussions on the use of dichlorvos as a biocide.

3.17 The COC heard a presentation from representatives of AMVAC Chemical Company on a possible MOA for forestomach tumours seen in a US National Toxicology Programe (NTP) gavage study in the mouse. This proposed that there is an interaction between dichlorvos and the corn oil vehicle used in the study. It was noted that there was no evidence of carcinogenicity by other routes of administration. It was also proposed that there is a threshold for tumour induction when dichlorvos is administered in corn oil.

3.18 Members agreed that there seems to be some interaction between corn oil and the test chemical, so it was plausible that the vehicle has some influence on the results of the NTP study and that dichlorvos could cause cancer through a threshold based mechanism. However, there were not sufficient data to

support the proposed MOA. The uncertainties in this case meant that the weight of evidence that dichlorvos was a potential human carcinogen was not strong. Nevertheless, the Committee's position on the risk assessment of carcinogens is that there needs to be clear evidence of a mode of action for tumour formation before it can move away from the default non-threshold assumption for substances that are genotoxic and carcinogenic. The Committee considered that the evidence was insufficient in this case and that, therefore, exposure should be as low as reasonably practicable (ALARP).

Systematic review of the epidemiological literature on para-occupational exposure to pesticides and cancer

3.19 In 2005, the Royal Commission on Environmental Pollution (RCEP) published a report on crop spraying and the health of residents and bystanders. This recommended a "…systematic review of the literature on pesticide spraying and human health…" The COT and COC commented on the RCEP report at the request of the Department for Environment Food and Rural Affairs and the Advisory Committee on Pesticides and published a joint statement in 2006. In this, the COT agreed that an epidemiological review of paraoccupational exposure to pesticides should be undertaken. The COC was therefore asked to review the relevant epidemiological literature on cancer.

3.20 In 2010, the COC considered a systematic review of the relevant literature which included a detailed meta-analysis of the available case-control studies. A number of different cancer types and exposure scenarios were reported in the case-control studies, which made comparison of these papers difficult in meta-analysis A meta-analysis was also performed for a small group of studies reporting on 'haematopoietic cancers' in children.

3.21 After reviewing the available data and analyses, the Committee considered that there was limited evidence for a weak positive association with maternal para-occupational exposure to pesticides and childhood leukaemia. There was insufficient evidence to determine whether this is causal, nor the likely candidate pesticides.

3.22 The COC noted that, although beyond the scope of the present review, studies investigating occupational exposure to pesticides, where exposure would be higher and better characterised, would be of great benefit in interpreting the significance of the weak effect suggested by this meta analysis. However, one Member noted that even the occupational studies suffered from poor exposure assessment.

3.23 A detailed statement is expected in 2011.

Guidance statements

3.24 During 2010, the COC adopted a proposal to change the way in which technical guidance on the risk assessment of carcinogens is presented on the COC website. At present, guidance is presented in a stand-alone booklet and is also spread throughout minutes and certain statements. The drawbacks of this approach are that valuable advice can be difficult to access and it is not always apparent when it is out of date. Furthermore, it can be time-consuming to reach a consensus on complex and comprehensive guidance booklets and specific elements of the guidance may soon become out of date; these elements will remain out-of-date until the next opportunity arose to review and revise the entire document. The proposed changes aim to improve accessibility of up-to-date advice, ease timely review, and make it easier to reference specific parts of COC guidance.

3.25 The new system will comprise an overarching statement which will provide an 'executive summary' of the advice, and a series of guidance statements on specific aspects of the risk assessment of carcinogens. The overarching statement will undergo regular updates as each detailed guidance statement is revised to reflect the best available scientific practice as it evolves. The Committee recognises that there will be a need to identify old versions of statements which have been updated and these may be kept in an archive. It also recognises that, currently, it provides no advice on the interpretation of epidemiology studies, and how these contribute to the weight of evidence in a carcinogenicity risk assessment, and intends to include such advice in one of the guidance statements.

2010 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

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Dr D Benford BSc PhD	Joint Scientific Secretary – Food Standards Agency
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Ms S Kennedy	Administrative Secretary– Health Protection Agency

Declaration of COC members interests during the period of this report
(an up-to-date version can be found on the COC website)

Member	Personal Interest		Non-personal Interest	
	Company	Interest	Company	Interest
Professor D H Phillips (Chairman)	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder	AstraZeneca	Research Support
Dr C Allen	NONE	NONE	NONE	NONE
Professor A Boobis OBE	BanK Santander SA Barclays Bank BG Group BT Group Centrica Iberdrola SA National Grid Lloyds Endura Fine Chemicals	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy	GlaxoSmithKlin FSA DoH HPA Commission of the EU (FP6) Medical Research Council CEFIC - LRI ESRC PhD Elsevier JMPR JECFA (vet drugs) EFSA PPR Panel (Panel on Plant Protection Products & their Residues) EFSA CONTAM Panel (Panel on chemical contaminants in the food chain) ECETOC Task Force on Guidance for Classification of Carcinogens under GHS EFSA Scientific Committee	Research Support Studentship Editor-in-Chief Food & Chemical Toxicology Member Member of

			Working Group on Risk-Benefit Assessment EFSA Scientific Committee Working Group on the Benchmark Dose ILSI HESI, ILSI Europe & ILSI Research Foundation Working Groups on generic risk assessment issues	 Unpaid member of Board of Trustees
Dr P Carthew	Unilever	Salary	Gwathmey(USA)	Consultant
Professor P B Farmer	Santander Foreign & Colonial Friends Provident Tototrak ILSI HESI EFSA	Shareholder Shareholder Shareholder Shareholder Committee Member Member of Scientific Panel	Van Geest Foundation	Research support
Mrs R Glazebrook	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE
Dr P Greaves	Actelion Pharmaceuticals Ltd (Switzerland) Astellas Pharma AstraZeneca INEOS Healthcare Nono Nordisk (Denmark) Pfizer Shire Pharmaceutical Synosia Therapeutics (USA) Teva Pharmaceuticals (Israel)	Consultant Consultant Consultant Consultant Consultant Consultant Consultant Consultant Consultant		
Ms D Howel	NONE	NONE	NONE	NONE
Dr D Lovell	National Grid Plc Pfizer	Shareholder Share Options & Pension	AstraZeneca National Grid Plc	Spouse is shareholder
Dr C Powell	GlaxoSmithKline	Salary & Shareholder		
Dr P Vineis	NONE	NONE	NONE	NONE

Dr N Wallis	Pfizer	Salary & Shareholder	NONE	NONE
Dr L Wright	AstraZeneca	Salary & Shareholder	NONE	NONE