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 2011, the Committee held two meetings and considered a number of items. At the request of the Department for Education, we began a consideration of the relative vulnerability of children to asbestos. This will clearly be a challenging item and I am grateful to the members of the Committee for their suggestions as to how we should go about it, and of information and appropriate individuals to assist us.

The Committee also responded to a request from the Department of Health for its view on the potential effects of climate change on the risk of cancer. I am grateful again to members for the ideas they contributed in response to this request. I also recognise the continued support of the secretariat and the value of the draft papers which they provide. I look forward to working with them on new challenges in 2012.

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BA PhD DSc FRCPath

COC evaluations

Climate change

3.1 During 2011, the COC was asked by the Department of Health to provide advice on climate change. It made a number of suggestions as to both the potential beneficial and adverse effects of climate change on the risk of cancer, as given in the table below. Any impacts on incidence of cancer due to climate change are likely to be long term, due to the protracted natural history of the disease(s).

Consequence of climate change	**Possible beneficial effect**	**Possible adverse effect**
People spend more time outdoors	More scope for exercise	Increased exposure to UV radiation leading to higher rates of skin cancer
	Increased levels of endogenous vitamin D	Increased consumption of food cooked outdoors which may contain carcinogens (eg barbecued food contains relatively high levels of nitrosamines)
	Decreased exposure to indoor air pollution	Increased exposure to outdoor air pollution
		More opportunity to smoke (no smoking ban outdoors)
Changes in air quality	Decrease in emissions due to domestic/indoor heating	Deterioration of urban air quality from industrial and traffic emissions with increasing temperatures. Effect of climate on composition of atmospheric particulates. Increase in emissions due to energy demand for widespread use of air conditioning.
Changes in food grown or available in the UK	Increased availability and consumption of fresh fruit and vegetables Changes in nutritional or residue content of food of animal origin	Increased levels of mycotoxins in food Changes in nutritional or residue content of food of animal origin Availability of different staples e.g. highly spiced foods leading to higher incidence of cancer of GI tract.
		Changes/increases in pesticide use
Spread of parasites from warmer countries	None	Increase in cancer associated with parasitic infection or use of chemicals to destroy parasites
More insect infestations indoors	None	Higher exposure to pesticides used to treat infestations

Major weather incidents e.g. flooding	None	Effects on contaminant dispersion, microorganism growth, water contamination.
Increasing salinity of groundwater and surface water as sea levels rise	None	Increased levels of salt consumption in food and water lead to increased risk of stomach cancer

Dichlorvos

3.2 Dichlorvos (2,2-dichlorovinyl dimethyl phosphate) is an insecticide acting by acetylcholinesterase inhibition. The genotoxicity and carcinogenicity of dichlorvos were evaluated by the COM in 2002, with the assistance of co-opted COC members. 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.

3.3 In 2010, 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. Members concluded that there were not sufficient data to support the mode of action (MOA) for forestomach tumours in a US National Toxicology Programme (NTP) mouse gavage study on dichlorvos which was proposed by AMVAC Chemical Company. The Committee's position on the risk assessment of carcinogens is that there needs to be clear evidence of a MOA for tumour formation before it can move away from the default non-threshold assumption for substances that are genotoxic and carcinogenic. The evidence was insufficient in this case and, therefore, it recommended that exposure should be as low as reasonably practicable (ALARP).

3.4 AMVAC subsequently submitted a number of further comments in the form of a technical note. The COC discussed these comments at the April 2011 meeting. The note suggested that studies by Wooder and Wight (Acta Pharmacol et Toxicol, volume 48, suppl V: pp 51-55, 1981) were extremely important in demonstrating that dichlorvos does not react with DNA *in vivo*. This paper was subsequently reviewed by two members with appropriate expertise and they agreed that there was no inconsistency between the results and the conclusion of the COM that dichlorvos should be regarded as an *in vivo* mutagen at the site of contact. Overall, the COC confirmed the conclusions it had made in 2010.

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

3.5 In 2010, the COC considered a scoping paper which reported ongoing activity in the area of genomics, environmental exposure assessment and gene-environment interaction. 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 agreed that the next step should be to compare, for a specific endpoint, GWAS studies and good quality studies investigating specific gene-environment interactions.

3.6 At the April 2011 meeting, the Committee discussed a paper on GWAS on bladder cancer and colorectal cancer. In response to specific questions posed in the paper, the Committee concluded as follows:

3.7 Overall, it was thought that GWAS have been useful but it would be difficult to use these data at this stage without clear understanding of the functional links and biological relevance. The research had now begun to focus on Exposure Wide Association Studies (EWAS) or the "Exposome".

3.8 The Committee was not yet clear how GWAS would inform the assessments of the COC other than on a case-by-case basis. For example, in a couple of studies, strong associations have been found between single nucleotide polymorphisms (SNPs) in or close to genes for xenobiotic metabolising enzymes and certain cancer types. This would support the involvement of environmental chemicals in the cancer process. However, there are endogenous substrates for many of these enzymes, so the findings would have to be considered within the broader context of all available information. Such studies are likely to have most impact on the assessments of the COC if the specific genes involved in the associations observed can be identified, and their biological relevance determined. The COC agreed that further development of the studies is needed and that some guidance on interpretation would be helpful.

3.9 Currently, the Committee did not consider that the findings of the GWAS described shed any light on the environmental causes of colorectal or bladder cancer. It was thought that EWAS were more likely to be useful.

3.10 Members were interested to know if GWAS could provide information about the epidemiology of cancer clusters. It was recommended that a watching brief was maintained in this area.

Municipal waste incinerators

3.11 In the late 1990s, the Committee discussed a study by the Small Area Health Statistics Unit (SAHSU) on cancer incidence near municipal waste incinerators (MWI) in Great Britain and published a statement which concluded that *'any potential risk of cancer due to residency near to a municipal solid waste incinerator was exceedingly low and probably not measurable by the most modern epidemiological techniques.''* A second statement was published in 2009 after a review of literature published since 2000 which concluded that *''there is no need to change the advice given in the previous statement in 2000, but the situation should be kept under review''*.

3.12 In 2011, the Committee considered three further papers on this topic published since the 2009 review. One reported a positive association between living near a MWI in Besancon, France and non-Hodgkin's lymphoma (NHL). The other two

studies were based in Italy and Brazil and showed a negative association between living near a MSWI and cancer incidence.

3.13 The COC recalled that it has previously seen papers on the incinerator in Besancon, France and had noted that, for many years, emissions of PCDDs and PCDFs from this incinerator were reported to be far higher than is currently permitted. The Committee noted issues with the methodology in this paper and also commented on the difficulties with histological classification of NHL. The evidence provided was considered to be weak overall. Problems were also noted in the other two studies. Overall, the Committee considered that there was no change in the position given in its previous statement.

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

3.14 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.

3.15 In 2010, the COC considered a systematic review of the relevant literature which included a detailed meta-analysis of the available case-control studies and began to draft a statement. This statement was completed in 2011 and the Committee agreed the following conclusions:

i) There is limited evidence for a weak positive association between para-occupational exposure of children to pesticides and haematopoietic cancer.

ii) Recent meta-analyses support an association between maternal prenatal exposure to pesticides and childhood leukaemia.

iii) There is insufficient evidence to determine whether the observed association is causal, nor the likely candidate pesticides.

iv) The conclusion reached regarding para-occupational exposure to pesticides in this statement related to the exposures considered in the relevant studies and should not be extrapolated to current exposures of residents and bystanders.

v) No specific chemicals or populations were identified that would warrant further investigation by the Advisory Committee on Pesticides at this time.

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

The role of miRNA related effects and chemicals on cancer

3.17 Ribonucleic acid (RNA) has a variety of functions in a cell and is found in many organisms. RNA and deoxyribonucleic acid (DNA) differ functionally. DNA primarily serves as the storage material for genetic information. RNAs are versatile molecules capable of an array of functions. In recent years many new small functional RNAs have been found. RNA is usually thought of as messenger RNA that serves as a template for translation of genes into proteins. In contrast, functional and non-coding RNA molecules are transcribed from a DNA sequence but not translated into proteins. The encoding DNA sequence is often referred to as an RNA gene.

3.18 In 2009, the COC considered a review of the role of RNA mechanisms in cancer development. One area of particular interest was the role played by small functional RNA molecules collectively called microRNAs (miRNAs) in carcinogenesis. At the April 2011 meeting, the Committee considered a review of 25 publications which described investigations of the influence of environmental chemicals on miRNA expression in cancer. These studies were considered to give a good picture of the field although there were some uncertainties with regards to interpretation of the studies. Also, it was not clear how the role of miRNA and related effects could be incorporated into cancer risk assessments nor how it would be useful as a diagnostic tool. The Committee considered that, currently, miRNAs would be less sensitive biomarkers of exposure than DNA adducts.

Horizon scanning

3.19 Due to cancellation of the November meeting, the annual horizon scanning item was postponed to January 2012 and will be reported in the 2012 Annual Report.

Ongoing work

Alcohol attributable burden of cancer

3.20 The COC reviewed the carcinogenicity of alcoholic beverages in 1995 as part of the health input to the Interdepartmental Working Group on the Sensible Drinking Message. From 2002 to 2004, the COC conducted a further review on alcoholic beverages and breast cancer. As part of this, the Department of Health commissioned a systematic review and subsequent meta-analyses from Imperial College Department of Epidemiology and Public Health which aimed to determine the magnitude of any association between drinking alcohol and primary breast cancer and to estimate the population attributable risk (PAR). Assuming causality and that 1 unit of alcohol contains 8 g ethanol, it was calculated that 6.0% (confidence interval 3 to 9%) of breast cancers reported in the UK each year could be prevented if drinking was reduced to a very low level (i.e. less than 1 unit/week).

3.21 At the July 2011 meeting, the Committee saw a recently published paper which estimated the alcohol attributable fraction of cancer in eight European countries (Schutze M et al. British Medical Journal, volume 342:d1584 June 2011). The

proportion of cancer cases attributable to former or current alcohol use in men aged >15 years was 10% (confidence interval 7 to 13%) and in women was 3% (confidence interval 1 to 5%). For breast cancer in women, it was 5% (2-8%).

3.22 The paper was considered to be of good quality because it reports the results of a large study with a relatively good exposure assessment and stable estimates. Members were also made aware of another recent publication from a French group which found that current alcohol consumption guidelines are inadequate for the prevention of cancer and that there was no safe level of alcohol consumption. It was suggested that the Committee should issue a statement again in light of the recent publications, to make its position clear.

Asbestos

3.23 Asbestos is a well known carcinogen which can cause both mesothelioma and lung cancer. Asbestos was used in the past in the building of homes, schools and other buildings and hence there is a potential for individuals to be exposed to asbestos from this historical use. At the July meeting, the Committee was informed about an independent advisory group called the "Asbestos in Schools Steering Group" which reports to the Department for Education (DfE). The Steering Group aims to promote effective management of asbestos in schools and to contribute to the development of guidance on such management. Following discussions in this Group, the DfE had asked the Department of Health for a study of the risk of asbestos to children and the Department had facilitated a DfE request for advice from the COC on the relative vulnerability of children to asbestos.

3.24 Initially, the COC was asked to advise on the appropriate strategy to take forward a consideration of this issue. The following approach was agreed:

i) to consider the recent advice of the Health and Safety Executive's scientific advisory committee, the Working Group on Action to Control Chemicals (WATCH), on the risks from low level exposure to asbestos in adults
ii) to consider reviews of any epidemiological literature or case-studies on children exposed to asbestos, of data from developing countries where children are occupationally exposed to asbestos and the development of mesothelioma in later life, and of animal data on the comparative differences between the effects of juvenile versus adult exposure to asbestos (if available)
iii) to review information on the levels of asbestos found in school buildings so as to provide an exposure perspective to the discussions
iv) to consider differences between adults and children in respiratory physiology, immunology and dosimetry
v) to co-opt experts from fields such as juvenile respiratory physiology, differences in inflammatory cell involvement between adults and children in the responsiveness to inhaled fibres, or asbestos epidemiology or pathology.

3.25 A statement is expected in 2012.

The carcinogenicity of carbon nanotubes

3.26 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. There is some concern that carbon nanotubes might have carcinogenic potential analogous to asbestos and in 2010 the COC heard a presentation from Professor Ken Donaldson of Edinburgh University on his work on CNT and discussed this issue with him. In 2011, the COC discussed a then pre-publication paper sent by Professor Donaldson on "Length dependent retention of carobn nanotubes in the pleural space of mice inititates sustained inflammation and progressive fibrosis on the parietal pleura (Americal Journal of Pathology, volume 178(6): pp 2587-2600, June 2011). The Committee considered this to be useful and discussed how it could help with the performance of risk assessments. It expressed continued interest in this work.

Guidance statements

3.27 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, which has several drawbacks. 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. 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.

3.28 During 2011, the COC made progress with the overarching statement, introducing new concepts such as the Mode of Action, Human Relevance Framework and Margin of Exposure. In the context of this guidance statement, the Committee considered risk assessment paradigms used by different organisations. These describe the individual steps in the risk assessment process. The COC decided to base its paradigm on one published by the US National Academy of Sciences in 1983 which specifies the different stages as hazard identification, hazard characterisation, exposure assessment and risk characterisation.

3.29 The overarching guidance statement will be published in 2012.

2011 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Chair

Professor David H Phillips BA PhD DSc FRCPath
Professor of Environmental Carcinogenesis, King's College London

Members

Dr Carolyn Allen BSc MSc PhD
Non-specialist Member

Professor Alan Boobis OBE BSc PhD CBiol FIBiol
Section of Experimental Medicine and Toxicology, Division of Medicine, Imperial College London

Dr Philip Carthew BSc MSc PhD FRCPath
Senior Pathologist, SEAC Toxicology Unit, Unilever

Professor Peter B Farmer MA DPhil CChem FRSC
Professor of Biochemistry, Cancer Studies and Molecular Medicine, Cancer Biomarkers and Prevention Group, Biocentre, University of Leicester

Mrs Rosie Glazebrook MA
Non-specialist Member

Dr Peter Greaves MBChB FRCPath
Consultant Pathologist and Honorary Senior Lecturer, Department of Cancer Studies & Molecular Medicine, University of Leicester

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Principal Epidemiologist, Institute of Occupational Medicine

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Global Drug Safety, Merck Serona SA Geneve

Dr Lindsay Wright PhD
Team Leader in General Toxicology Sciences, Therapy Area Toxicologist for Infection Therapy Area, Project Team Representative, AstraZeneca

Secretariat

Ms F Pollitt MA DipRCPath	Joint Scientific Secretary – Health Protection Agency
Dr D Benford BSc PhD	Joint Scientific Secretary – Food Standards Agency
Dr L Hetherington BSc PhD	Scientific – Health Protection Agency
Mr J Battershill BSc MSc	Scientific– Health Protection Agency
Ms S Kennedy	Administrative Secretary – Health Protection Agency

Declaration of COC members' interests during (2011) 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 Takeda	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy		
Dr C Allen	NONE	NONE	NONE	NONE
Prof A Boobis OBE	Bank Santander Barclays Bank BG Group BT Group Centrica Iberdrola SA National Grid Lloyds Endura Fine Chemicals Astra Zeneka GlaxoSmithKline DuaneMorris	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancies	Food Standards Agency Department of Health Health Protection Agency Medical Research Council Medical Research Council GlaxoSmithKline ILSI, ILSI HESI & ILSI Europe Board of Trustees/ Directors ILSI HESI Risk 21 project ILSI HESI, ILSI Europe & ILSI Research Foundation Working Groups on generic risk assessment issues. JMPR JECFA (vet	Research Contracts PhD studentships Trustee/Director (non-remunerated) (past Chair of HESI) Co-Chair Member Chair/Member

			drugs) EFSA CONTAM Panel (Panel on chemical contaminants in the food chain) EFSA PPR Panel Working Groups on Cumulative Assessment Groups for Pesticides; Risk Assessment of Pesticide Metabolites EFSA working group on Identification of Emerging Risks EFSA Scientific Committee Working Group on Threshold of Toxicogical Concern DG SANCO SCHER Working Group on Mixtures of Chemicals WHO IPCS Working Groups on Chemical Mixtures and on Mode of Action FP7 COSMOS Project Scientific Advisory Board of FP6/7 projects: PREDICT – IV ACROPOLIS and HEROIC Science Advisory Board, Swiss Centre for Applied Human Toxicology, Basel, Switzerland.	
Dr P Carthew	Unilever	Salary	Gwathmey, Cambridge USA	Consultancy work

Prof P B Farmer	Santander Bradford & Bingley Foreign & Colonial Friends Provident Torotrak EFSA ILSI HESI	Shareholder Shareholder Shareholder Shareholder Shareholder Member of Scientific Panel Committee Member	Van Geest Foundation	Research support
Mrs R Glazebrook	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE
Dr Peter Greaves	Actelion Pharmaceuticals Ltd, Allschwil, Switzerland. Arena Pharmaceuticals, Inc., San Diego, California Astellas Pharma Europe Ltd Daiichi Sankyo, Edison, New Jersey Experimental Pathology Laboratories Inc., Sterling, Virginia GlaxoSmithKline, Ware Hyperion Therapeutics, Inc., San Francisco, California Johnson & Johnson Pharmaceutical Research & Development LLC, Raritan, New Jersey Novo Nordisk,A/S, Malov, Denmark Shire Pharmaceutical Development Ltd, Basingstoke, UK Sun Coast Tox Inc., San Diego, California.	Consultant	NONE	NONE

Dr David Lovell	National Grid plc Pfizer	Shareholder Shareholder	AstraZeneca National Grid plc	Spouse shareholder
Dr B G Miller	(Iberdrola SA)	Shareholder	NONE	NONE
Dr Christopher Powell	GlaxoSmithKline	Shareholder and salary	NONE	NONE
Dr P Vineis	NONE	NONE	NONE	NONE
Dr N Wallis	Pfizer Merck Serona SA, Geneve	Shareholder Salary	NONE	NONE
Dr Lindsay Wright	AstraZeneca	Salary and shareholder	NONE	NONE