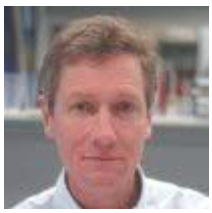
COMMITTEE ON THE CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

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/).

The COC held four meetings in 2012, because of the cancellation of the November 2011 meeting. During the year we were asked for advice by a number of Government departments or agencies. The Medicines and Healthcare Regulatory Agency (MHRA) asked whether the existing advice on the carcinogenic risks of polyurethane breast implants needed to alter in the light of a new review; the Food Standards Agency (FSA) sought advice on the possible carcinogenic hazard to consumers from insulin-like growth factor in the diet and we contined our consideration of the relative vulnerability of children to asbestos, at the request of the Department for Education. Also, we continued the review of our guidance on carcinogenic risk assessment and published two new guidance statements.

As always, I am grateful to members of the committee for the invaluable advice they have provided during the year and to the secretariat for their support. I look forward to working with them on more challenges in 2013.

Professor David H Phillips
BA PhD DSc FRCPath

COC Evaluations

COM review on cell transformation assays

At the horizon scanning discussion in January 2012, the COC suggested that there should be a consideration of cell transformation assays as an *in vitro* screen for carcinogenicity given the renewed interest in these assays and a recent report from the European Centre for the Validation of Alternative Methods. It was noted that cell transformation assays are formally within the remit of the COM and so it was referred to that committee. At its November 2012 meeting, the COC discussed the resultant COM statement.

The COC considered the difficulties in the methodology used in these assays. These included the length of time for the automated process to produce results, the problems with pH, and inconsistencies between protocols and the selectivity and sensitivity of different cell lines. The committee thanked the COM for its thorough review of the topic.

ILSI/HESI workshop on less-than-lifetime exposure to carcinogens.

In 2009, the COC had expressed an interest in the outcome of a workshop to be held by the International Life Sciences Institute Health and Environment Institute (ILSI/HESI), which aimed to develop a framework for assessing the risk from less-than-lifetime exposures to carcinogens. At its January 2012 meeting, the committee considered a published paper which presented the proposed framework ('A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens' - Felter et al 2011, Critical Reviews in Toxicology volume 41, number 6, pp 507-544). The framework consists of a number of sequential questions laid out as a decision tree and the committee considered that the guidance would encourage case-by case judgements, rather than the application of a prescribed process. It was noted that the approach included a large number of general assumptions, and concerns were raised about the higher doses administered in studies with shorter dosing regimens and the possibility of secondary modes of action. It was considered that extrapolation from less-than-lifetime studies to assess longer-term exposure was likely to be over-precautionary. It was suggested that useful information might be obtained from human studies of patients treated for Hodgkin's disease and secondary cancers.

Overall, the COC considered that, as general guidance, the ILSI/HESI framework was informative but members expressed concern that the underlying approach was directed towards the US approach to cancer risk assessment, which estimates cancer risk by low-dose extrapolation of animal data, and which the COC does not endorse.

Polyurethane-coated breast implants

The COC considered the safety of polyurethane-coated breast implants in 1991 and 1994 when studies had shown that a degradation product of the polyurethane foam, 2,4-toluenediamine (2,4-TDA), should be regarded as a probable genotoxic carcinogen. At the time, the Medicines and Healthcare Products Regulatory Agency (MHRA) had advised that the benefits of using these implants did not outweigh the small, unquantifiable carcinogenic risk. At the November meeting, the MHRA asked the COC to consider an updated review, produced by the Agency, of the relevant literature on the risks and benefits of these implants, and to consider whether the advice should be changed.

It was noted that old animal carcinogenicity data showed that 2,4-TDA was a potent carcinogen in both rats and mice at low doses and that the review had found few new studies of relevance. Localised, low-grade fibrosis may also be a concern as implants could be in place for 10 years or more. Members also commented on a Derived Minimal Effect Level (DMEL) for 2,4-TDA calculated in the report and expressed concern about uncertainty in the Physiologically Based Pharmacokinetic Modelling (PBPK) carried out.

In conclusion, it was agreed that the new information did not alter the Committee's position on these breast implants and it was recommended that the MHRA did not alter its advice on their carcinogenicity.

Horizon scanning

The COC undertakes "horizon scanning" exercises at regular intervals with the aim of identifying new and emerging issues which have the potential to impact on public health.

Due to the cancellation of the last meeting in 2011, the 2011 Horizon scanning exercise was undertaken in January 2012 and is reported here.

Two new topics were identified by the Secretariat at the 2011 exercise and these were considered by the Committee, together with those outstanding from the 2010 exercise. From these and items suggested by Members, the COC decided that the following items should be taken forward:

- Vitamin E and prostate cancer risk – considered to be high priority
- *In utero*/whole life exposure model of carcinogenesis – to be covered in the forthcoming new Guidance Statements
- Cell transformation assays as an *in vitro* screen for carcinogenesis – this was considered to be within the remit of the COM
- Exposure to environmental tobacco smoke and childhood cancer
- Mononuclear cell leukaemia in the Fischer 344 rat
- The use of Zebrafish in mechanistic studies

In the 2012 exercise a number of new topics were considered together with those outstanding. The following priorities were assigned:

High priority:

- Epigenetics and cancer
- Relevance of PPAR-α agonism to humans
- Alcohol attributable burden of cancer incidence
- Nanomaterials

Medium/high priority:

- In utero/'whole life' exposure models of carcinogenesis and Alternatives to the 2-year bioassay - these two items will be considered as part of the forthcoming new Guidance Statement G7 (Alternatives to the 2-year bioassay)
- Thresholds of genotoxicity – to take forward potentially as a topic of interest in a joint COT/COC/COM scanning meeting

Medium Priority

- Mode of action framework update
- Environmental tobacco smoke exposure in childhood and cancer risk
- Dose response modelling in epidemiology studies - this will be covered as part of the Guidance Statement G2 (Interpretation of Evidence of Carcinogenicity in Humans)

Low Priority

- Mechanistic studies in Zebrafish

Ongoing work

Relative Vulnerability of Children to Asbestos

Asbestos is a well known carcinogen that 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. An independent advisory group called the "Asbestos in Schools Steering Group" aims to promote effective management of asbestos in schools and to contribute to the development of guidance on such management. The group reports to the Department for Education (DfE). 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. In July 2011, COC members agreed an appropriate strategy to take forward a consideration of this issue.

During the meetings in 2012, the COC considered a number of papers which reviewed information relevant to this issue. These included a review of the epidemiological literature/case-studies on childhood exposure to asbestos and the risk of developing mesothelioma in later life; 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; and a review of the available animal data on the comparative differences between the effects of juvenile versus adult exposure to asbestos. A review of the levels of asbestos found in school buildings provided an exposure perspective to the discussions, as did a paper on the levels of asbestos found in residences, including houses and flats, which provided information on background levels of asbestos in homes. At the July meeting, the Committee considered the differences between adults and children in terms of respiratory physiology, immunology and dosimetry. Members also considered a non-peer reviewed paper entitled "Effect of children's age and life expectation on mesothelioma risk", prepared by Robin Howie Associates, and submitted by Mr Lees of the Asbestos in Schools group.

During the year, the COC sought the view of two experts to aid its consideration. In July, it heard from a pediatric respiratory consultant, Professor Andrew Bush (Professor of Paediatric Respirology at Imperial College & Consultant Paediatric Chest Physician at the Royal Brompton & Harefield NHS Foundation Trust), working in the field of juvenile respiratory physiology, to aid the discussion of the differences between the respiratory system in adults and children. Professor Jonathan Grigg (Professor of Paediatric Respiratory and Environmental Medicine at Barts and the London School of Medicine, Queen Mary University of London) attended the November meeting to provide an insight on whether it was possible to extrapolate information on the effects of particulates in the juvenile lung to fibres. He presented some modelling data generated specifically for the Committee's assessment by Dr Robert Sturm (Division of Physics and Biophysics, University of Salzburg).

A first draft of a statement, based on the papers and the Committee's deliberations since July 2011, was considered in November. The final statement is expected to be agreed in 2013.

IGF-1: Possible carcinogenic hazard to consumers

Interleukin Growth Factor 1 (IGF-1) is a growth factor which has a variety of biological effects including the promotion of cell division and growth. It has been proposed that exposure to dietary IGF-1 could increase the risk of certain cancers.
The COC is considering an extensive range of data which covers dietary absorption, levels of IGF-1in food and the association between blood levels of IGF-1 and the risk of certain types of cancer. The review is ongoing and it is hoped that it will be completed by the end of 2013.

Vitamin E and prostate cancer

In 2011, analysis of results from the selenium and vitamin E cancer prevention trial (SELECT), which investigated the chemoprotective effects of selenium and vitamin E, suggested that vitamin E supplementation in healthy men significantly increased the risk of prostate cancer; the results of this study contrasted with the findings of other authors, who have reported both a protective effect and no effect.

The Food Standards Agency has asked that the Committee review the information available on vitamin E and prostate cancer, including epidemiological, animal and *in vitro* studies on this topic. The review is ongoing and it is hoped it will be completed in 2013.

Guidance statements

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.

During 2012, the COC completed the overarching statement G1: "A strategy for the risk assessment of chemical carcinogens". It also completed a statement on risk characterisation methods for carcinogens, which discusses the approaches that the committee recommends for the risk characterisation of non-threshold and threshold carcinogens. The guideline also discusses other approaches that are not endorsed by the COC, and gives the reasons why.

A guideline on the use of biomarkers in carcinogenic risk assessment was discussed and is expected to be published in 2013.

DECLARATION OF INTERESTS DURING (2012) THE PERIOD OF THIS REPORT

	Personal Interest		**Non-personal Interest**	
Professor David H Phillips (Chairman)	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid Takeda	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy		
Dr Carolyn Allen	None	None	None	None
Prof Alan Boobis OBE	Bank Santander Barclays Bank BG Group BT Group Centrica Iberdrola SA National Grid Lloyds Endura Fine Chemicals Astra Zeneca GlaxoSmithKline DuaneMorris Coca-Cola (from Oct 2012)	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancies	Food Standards Agency Department of Health Health Protection Agency Medical Research Council European Chemical Industry Council – Long range Initiative Medical Research Council GlaxoSmithKline ILSI, ILSI HESI & ILSI Europe Board of Trustees/ Directors ILSI HESI Risk 21 project	Research Contracts PhD studentship Trustee/Director (non-remunerated) (past Chair of HESI) Vice-president of ILSI Europe Co-Chair

			ILSI HESI, ILSI Europe & ILSI Research Foundation Working Groups on generic risk assessment issues.	Member
			JMPR	Chair/Member
			JECFA (vet 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 Phil Carthew	Unilever	Salary	None	None
Prof Peter B Farmer (to 31.10.12)	Santander Bradford & Bingley Foreign & Colonial Torotrak EFSA ILSI HESI	Shareholder Shareholder Shareholder Shareholder Member of Scientific Panel Committee Member	Van Geest Foundation	Research support
Mrs Rosie 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,	Consultant	EFSA ILSI	Member of Scientific Panel Committee Member

	Malov, Denmark Shire Pharmaceutical Development Ltd, Basingstoke, UK Sun Coast Tox Inc., San Diego, California. Biotie Therapies Inc., S. San Francisco			
Dr David Lovell	National Grid plc	Shareholder	AstraZeneca National Grid plc EFSA EFSA member ECVAM ESAC	Spouse shareholder Member & Vice Chair Working Group on Threshold of Toxicological Concern Working Group on Genotoxicity Testing Strategies Working Group on Statistical Approaches (Member & Chair) Member of various working Group Peer Review panels
Dr Brian G Miller	Iberdrola SA	Shareholder	None	None
Prof Julian Peto (from 1 April 2012)	None	None	None	None
Dr Christopher Powell	GlaxoSmithKline	Shareholder and salary	None	None
Dr Lesley Rushton (from 1 April 2012)	Friends Provident Northern Rock Epidemiological Advice relating to dermatitis study to Unilever. Epidemiological advice on study to Transport and General Workers Union Epidemiological review of occupational causes of malignant	Share holder Shareholder Consultancy Consultancy Expert witness	CONCAWE (Conservation of Clean Air and Water Europe) CEFIC (European Chemistry Council) Other grants from UK government	Research support Research support Research support

	melanoma.		agencies & departments e.g. Food Standards Agency, Health & Safety Executive. ECETOC Scientific Committee	External Committee member
Dr P Vineis (until 31 March 2012)	None	None	None	None
Dr Heather Wallace (from 1 April 2012)	Bank Santander SA BT Group	Shareholder Shareholder	None	None
Dr N Wallis	Pfizer Bristol Myers Squibb	Shareholder Salary	None	None
Dr Lindsay Wright (until 31 March 2012)	AstraZeneca	Salary and shareholder	None	None