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 2009, the Committee considered a number of interesting and challenging topics. These included the provision of advice to the Department of Health on current tests used to evaluate the carcinogenicity of tobacco products and being used to support claims made by manufacturers of new products, a review of recently published studies of cancer incidence around municipal solid waste incinerators; and further work on our ongoing risk assessment of the effects of combined exposures to chemical carcinogens. Also, we were asked by the Food Standard Agency’s Scientific Advisory Committee on Nutrition for our views on the evidence for the relationship between red and processed meat consumption and the risk of colorectal cancer. It is fortunate that the Committee possesses the wide range of expertise required to advise on such a variety of topics.

Ms Denise Howel, Dr Ruth Roberts and Dr David Shuker retired from the committee in 2009. I would like to thank them on behalf of the committee and secretariat for their valuable contributions over the years and to wish them well in the future. We welcomed a number of new members, with expertise in toxicology, pathology and medical statistics, with whom I look forward to working.

I would like to thank the members and secretariat of the Committee for the work they have undertaken during the past year. We look forward to new challenges in 2010.

Professor David H Phillips
BA PhD DSc FRCPath
COC evaluations

Carcinogenicity testing of tobacco products

3.1 The Department of Health asked for an update of the 2004 COC/COM/COT statement on the toxicity of tobacco products because of the increasing literature in this area and a growing concern about the strategies used for the carcinogenicity testing of tobacco products. There is no internationally agreed approach to the hazard assessment of these products and so the Department required scientific advice on the suitability of the tests used to evaluate the carcinogenicity of tobacco products and on the suitability of the toxicological data used to support the claims made by manufacturers of new products which purport to reduce harm to users.

3.2 The Committee was asked for advice in the following areas:

I. Whether the approaches currently used to evaluate the carcinogenic potency of tobacco and its products are suitable, and the inhalation and dermal carcinogenicity of tobacco smoke.

3.3 The Committee advised that some of the animal models used to assess the carcinogenic potency of tobacco had been discredited. Lung sectioning is not straightforward and delivery of whole smoke to the lungs is technically challenging because of difficulties in managing inhaled particle size. Skin may not be representative of other organs. Overall, these studies might help to identify and characterise some aspects of the hazard posed by these products, but it is not possible to use them as a basis for comparative risk assessment.

II. The validity of claims of reduced exposure, harm or risk posed by existing and novel tobacco products.

3.4 This discussion included modified products, potentially reduced exposure products (PREPs), novel nicotine delivery systems (such as e-cigarettes) and smokeless tobacco products. Members disagreed with the notion that the studies reviewed demonstrated a reduction in carcinogenic potential associated with a reduction in exposure to harmful substances. These studies did not support the hypothesis that these products are associated with a lower risk of overall carcinogenicity than conventional cigarettes, although there may be limited evidence for specific tumour types.

3.5 There was some uncertainty as to whether e-cigarettes only deliver nicotine in a vapour, or whether users of these products are exposed to other chemicals. If these products only contain nicotine, they would not be expected to contribute to exposure to tobacco derived carcinogens.

3.6 The Committee noted that, in developing approaches to assess the carcinogenic potential associated with the use of novel and existing products,
there may be a temptation to develop tests that are sensitive, but not necessarily predictive of the real risk. Using such tests would result in spurious claims. It may also be inappropriate to perform direct comparisons of products without taking into account changes in smoking behaviour that might be expected to occur once the use of the new product has become established. It was noted that, in a number of intervention studies where electrically heated cigarettes were used for up to 12 months, product use increased throughout the study with no apparent plateau.

3.7 Members agreed with the view of the World Health Organisation (WHO) i.e. that these products are not legitimate cessation aids for smokers trying to quit because they have not been adequately tested, nor to be proven nicotine replacement therapy (NRT) products. At present, there is no evidence to confirm safety or efficacy and there are no peer-reviewed studies on these products. However, it is possible that they could be smoking cessation aids, albeit with appropriate clinical studies and toxicity analyses.

**III. Suitability of the approaches used to assess the contribution of individual or mixed ingredients or additives to the overall toxicity of tobacco products.**

3.8 The Committee considered that the available studies used to assess the contribution of individual or mixed ingredients or additives to the overall toxicity of tobacco products are inadequate to assess the risks posed by conventional cigarettes, so it is not possible to assess the modulation of that risk resulting from inclusion of additives. The relationship between effect (an increase in biomarker) and exposure is also poorly understood. Furthermore, it is possible that additives might alter smoker behaviour, such as to increase product use; this increased exposure would be likely to result in an increased risk.

**IV. Whether there are validated biomarkers of effect for tobacco or its products**

3.9 The Committee considered that the development of biomarkers of harm for tobacco products, particularly in relation to cancer, was a laudable but an unrealistic goal. The carcinogenic mechanisms underlying tobacco carcinogenesis are very complex, and are likely to be different in the various target organs and tissues, so it will be very difficult to identify a suitable comprehensive biomarker of effect. The 'omics technologies might provide some alternatives but these would tend to be biomarkers of exposure, rather than effect. Metabonomics might be able to identify biomarkers of early effects in adequately designed prospective studies amongst smokers, although the Committee was sceptical about the likelihood of finding a suitable biomarker.
V. The proposed use of Cancer Risk Indices for the prioritisation of carcinogens in cigarette smoke.

3.10 The Cancer Risk Index (CRI) approach to tobacco carcinogenesis ranks constituents of tobacco smoke according to their toxicological hazard and concentration. It is proposed as a prioritisation method. Members questioned the aims of the CRI approach and how a prioritisation of carcinogens in tobacco smoke would be used. Since the available studies are inadequate to assess the risks posed by conventional cigarettes, it is not possible to assess the risks following removal of a specific carcinogenic element of the product. It would be very difficult to infer reduced harm on the basis of studies examining a limited number of endpoints.

3.11 Overall, the Committee concluded that, although it would be desirable to identify and remove carcinogenic components from tobacco products, it is not clear whether this would result in any reduction in harm. Concern was also expressed that the highly uncertain potential reduction in harm could be used to market these products to smokers who may have otherwise successfully given up smoking.

Non-Hodgkin's lymphoma

3.12 Malignant tumours of the lymphoid system, lymphoma, are divided into two major groups: Hodgkin's disease and non-Hodgkin's lymphoma (NHL). NHL is not a single disease but a mixture of disease entities. There are several schemes that have been used to characterise the disease. The majority of NHLs are of B lymphocyte origin, arising in lymph nodes. Treatment and prognosis depend on subtype.

3.13 NHL is the seventh most common cancer in men and the sixth most common cancer in women in the UK and statistics indicate that the incidence has increased since the 1970s. The COC has reviewed the scientific literature to assess whether there is any convincing evidence that environmental chemicals are responsible for the reported increase in the incidence of non-Hodgkin's lymphoma.

3.14 There are a number of suspected, non-chemical risk factors for NHL. The strongest and most well-established factors are characterised by dysregulation or suppression of immune cell (T-cell). These include specific infections such as HIV/AIDS, immune deficiency and persistent immune suppression following organ transplantation. However, risk factors for which there is strong evidence of an association are considered to account for only a small percentage of total NHL cases.

3.15 The Committee reviewed 57 studies of the association between NHL and exposure to environmental chemicals, including pesticides, organic solvents,
industrial chemicals, and chemicals associated with lifestyle. The following conclusions were reached:

I. There is limited evidence of an increased risk of NHL following nonoccupational exposure to polychlorinated biphenyls (PCBs). It would be valuable for the data on PCBs to be considered in more detail, preferably in the form of a meta-analysis or pooled analysis. However, any positive association with PCBs would not explain the trends in incidence of this cancer, given that PCB levels in the environment have decreased over the last few decades.

II. The available evidence on exposure to 1,3-butadiene and NHL does not provide convincing evidence of an association.

III. There is no clear evidence of an association between benzene exposure and NHL in the general population. One study has shown an increased risk of NHL from benzene in those with a family history of malignant haematologic neoplasms.

IV. After reviewing the available data, we conclude that there is no convincing evidence from epidemiological studies that environmental chemicals are responsible for the reported increase in NHL incidence which has occurred over the past 3 to 4 decades. As noted above, there is limited evidence of an association between NHL and non-occupational exposure to PCBs.

3.16 A statement can be found at:

Folic acid

3.17 From 2005 to 2007, the COC provided advice to the Scientific Advisory Committee on Nutrition (SACN) and the FSA on whether dietary folic acid intake is associated with increased cancer risk. The Committee concluded that, on balance, it was content with the recommendation by the SACN, and subsequent proposals by the FSA Board, to recommend to UK health ministers that there should be mandatory fortification of a food with folic acid, with controls on voluntary fortification and guidance on use of supplements, monitoring of the folic acid intakes and status of the UK population and postulated risks – including cancer incidence – and a review of the data on the benefits and possible risks 5 years after introduction of mandatory fortification. Members asked to be informed of the outcome of the 5 year review.

3.18 Subsequently, Members were informed that the Chief Medical Officer had decided to convene a special subgroup of the Scientific Advisory Committee on Nutrition (SACN) to examine further two papers on the potential adverse effects of folic acid on the risk of colorectal cancer and that the Chairman and
one member had been invited to participate in this working group. The group was presented with pre-publication data from a consortium of researchers conducting clinical trials on B-vitamins. In 2009, at the request of the COC Chairman, Dr Robert Clarke, the consortium co-ordinator, presented these pre-publication results to the Committee. The item was taken as reserved business and the details of the discussion will be published when the results of all the B vitamin trials are published, which is expected to be by the end of 2010.

Persistent environmental chemicals in human milk

3.19 The incidence of testicular cancer has been increasing gradually in many countries since the 1960s and the reasons for the increase are largely unknown. A review by the COC in 2006 identified no clear chemical aetiology. The incidence varies widely around the world and varies with ethnicity. In 2009, the COC reviewed a paper\(^1\) which noted that there is a three to fourfold higher incidence of testicular cancer in Denmark than in Finland and postulated that endocrine disrupting chemicals may be responsible for the increase in testicular cancer and that exposure to these chemicals may be higher in Denmark than in Finland. The paper described an ecological study which compared levels of endocrine disrupting chemicals in human milk samples taken from Danish and Finnish women who had been part of an earlier cohort study on cryptorchidism, although only milk from women who delivered a healthy, non-cryptorchid boys was included in the study. The authors reported that the levels of chemicals were generally higher in the Danish samples, where the concentration range of persistent organic pollutants was also much broader and included some quite high values. The authors concluded that the study revealed conspicuous differences between the levels of chemicals in Danish and Finnish human milk samples and that specific chemical signatures were found in the two countries. The COC was asked whether it agreed with this conclusion and for comments on the study.

3.20 The Committee commented that, since it was an ecological study, it was not possible to determine whether any association was causal and other systematic differences between the populations might explain the effects seen in testicular cancer rates. A number of reservations were expressed about the reporting of the analytical methods, the sample collection and processing, and the statistical analyses used. The Committee noted that it would be reasonable to expect that 6 out of 121 chemicals might be different between two national populations and that, in view of the classes of persistent organic pollutants that had been identified, it was reasonable to assume that there would be some correlation amongst many of the chemicals.

3.21 The COC concluded that, from the data provided, it might be possible to say that the chemical signature may be different when comparing the two sampled groups; however, it is not possible to infer that this signature is representative of the Danish and Finnish populations and, therefore, any associations should be regarded with caution.

**Municipal waste incinerators**

3.22 In light of recent public interest and new European Union (EU) legislation on emissions from plants which incinerate or co-incinerate waste. The COC updated its advice on cancer incidence near municipal solid waste incinerators (MSWIs). The COC last discussed this topic in the late 1990s following the publication of a study by the Small Area Health Statistics Unit on cancer incidence near incinerators in Great Britain and concluded. “The Committee was reassured that any potential risk of cancer due to residency (for periods in excess of 10 years) near to municipal solid waste incinerators was exceedingly low and probably not measurable by the most modern epidemiological techniques. The Committee agreed that, at the present time, there was no need for any further epidemiological investigations of cancer incidence near municipal solid waste incinerators.”

3.23 As of November 2008, there were 18 MSWIs in operation in England and Wales, one in operation on the Isle of Man and two in operation in Scotland. All of these MSWI are Energy from Waste (EfW) incinerators, generating energy such as heat and electricity as by-products. The by-products of the incinerator process may contain potentially toxic pollutants and emissions, which will contribute to background pollution levels. The Committee was informed that, since 1996, there have been significant cuts in emissions from incinerators in order to meet strict limits set by EU legislation. The EU Waste Incineration Directive (2000/76/EC, often termed “WID”), which applies to the incineration and co-incineration of both hazardous and non-hazardous waste, will further reduce the potential to pollute. The WID regulations introduced strict regulatory controls and minimum technical standards throughout the European Community for waste incinerators and co-incinerators which incinerate and co-incinerate waste. As a result, currently operating MSWIs are permitted to emit far lower levels of pollutants than were permitted in the past.

3.24 Six further relevant epidemiological papers had been published since the 2000 statement, three of which investigated cancer incidence around a single incinerator in France. Positive associations were reported between exposure

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2 Cancer incidence near municipal solid waste incinerators in Great Britain. COC statement COC/00/S1 - March 2000. [http://www.iacoc.org.uk/statements/Municipalsolidwasteincineratorscoc00s1march2000.htm](http://www.iacoc.org.uk/statements/Municipalsolidwasteincineratorscoc00s1march2000.htm)
to pollutants from MSWI (principally, PCDDs and PCDFs) and non-Hodgkin’s lymphoma (NHL), soft tissue sarcomas (STS), and childhood cancers. No association or a negative association was reported between emissions of PCDDs and PCDFs and invasive breast cancer. The Committee noted that all the epidemiology studies were carried out on incinerators in operation prior to the imposition of the current strict controls on emissions.

3.25 After reviewing the studies, the Committee decided that it was unable to draw conclusions from one of the studies and that only limited conclusions could be drawn from two further studies because they included emission sources other than MSWIs and failed to adjust for confounding factors. Three of the further studies were carried out around the same incinerator in France which was reported to emit far higher concentrations of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans than currently permitted. Although these studies indicated some evidence of a positive association between two of the less common cancers i.e. NHL and soft-tissue sarcoma and residence near to incinerators in the past, the Committee considered that the results could not be extrapolated to current incinerators, which emit lower amounts of pollutants. Moreover, they are inconsistent with the results of the larger study on cancer incidence around municipal incinerators carried out by the Small Area Health Statistics Unit. It concluded, therefore, that there was no need to change the advice given in the previous statement but that the situation should be kept under review.

3.26 A statement can be found at:  

**OECD Guidance Document for the performance of chronic toxicity and carcinogenicity studies**

3.27 The Organisation for Economic Cooperation and Development (OECD) is currently developing a guidance document for the performance of chronic toxicity and carcinogenicity studies, to support the relevant Test Guidelines. In 2008, Members had recommended that the UK should propose leading on the chapter on histopathology and this offer was accepted by the OECD. The scope of the chapter was later expanded to include all investigations. In 2009, the Committee commented on a draft outline for this chapter, which had been developed from existing OECD Guidance, using Society of Toxicologic Pathology Guidance documents, standard texts and published literature. It was agreed that the new Guidance Document should be drafted as a stand-alone document that replaces the previous OECD guidance. A number of comments were made on the document and Members offered to provide recent publications which would be more appropriate references for some
parts of the document. It was also recommended that a section on ophthalmoscopy be included in the chapter.

Scientific Advisory Committee on Nutrition Report on Iron and Health

3.28 During 2009, the Scientific Advisory Committee on Nutrition (SACN) sought advice from the COC on the evidence for the relationship between red and processed meat consumption and the risk of colorectal cancer (CRC), as part of the consultation on its draft Report on Iron and Health. This report summarised the available epidemiological and mechanistic evidence on this topic.

3.29 The Chairman of SACN Working Group on Iron provided a brief background of the draft report and informed the Committee that there were a number of uncertainties in the data. With reference to cancer, the draft SACN report concluded that red and processed meat is “probably” associated with colorectal cancer (CRC). The SACN advice was more moderate than that of the World Cancer Research Fund (WCRF) report on diet and cancer, which had concluded that red and processed meat is a “convincing” cause of CRC.

3.30 Members discussed the available studies and concluded that, although the majority of the studies indicate red and processed meat intake is associated with increased risk of CRC, the evidence is not unequivocal. It was noted that meat consumption varies with socioeconomic status and that eating meat is associated with many other lifestyle factors. Therefore, all studies will be subject to considerable confounding which is unlikely to be completely removed during epidemiological analysis, although residual confounding is unlikely to entirely explain the observed increased risk reported in most studies. Genetic predisposition is unlikely to be a potential confounder, except in particular circumstances. However, it is possible that dietary preferences might be influenced by perceived familial susceptibility to disease. Members advised that any recommendations should take account of the biological and epidemiological limitations of the evidence base.

3.31 The various potential biological mechanisms for the association between red and processed meat and CRC risk was considered. It was noted that the hypothesis that the mechanism may be heterocyclic amines (HCA) produced during the cooking of meat had weakened. Recent studies had failed to show an association between well-cooked meat and cancer and the Margin of Exposure between carcinogenic dose of HCAs in experimental studies and human exposure is large. Members noted that there was not strong evidence linking CRC risk with N-nitroso compounds, which are found in processed meats, and it was noted that endogenous formation can exceed exogenous exposure. Members also considered oxidative stress associated with the iron contained in meat, although it was noted that the majority of dietary iron
comes from vegetables, supplements and fortified foods. Overall, although each mechanism was considered plausible, none was supported by robust evidence.

3.32 The Committee made a number of comments on the wording of the SACN draft conclusion but supported the view that there is an association between the consumption of red and processed meat and CRC, although it is not known whether the relationship is causal. It was suggested that the conclusion should be re-worded to make this clearer and that this should also feature prominently in risk communication. Members also concluded that, even with the residual uncertainties, any risk appeared to be small.

3.33 WHO/IPCS Harmonization Project: Framework Document on Risk Assessment of the combined exposures to multiple chemicals

3.34 At the July meeting, the Committee’s views were invited on a document produced by the World Health Organisation (WHO) International Programme on Chemical Safety (IPCS) entitled ‘Risk assessment of the combined exposures to multiple chemicals’. Comments had been invited from groups and individuals with an interest in the area.

3.35 It was noted that the methodology described was only applicable to chemicals acting by a common mode of action. Members considered it useful that the document developed two parallel tiered approaches for exposure and hazard assessment but commented that discussion and development of hazard index/quotient would have been helpful. It was noted that the approach was intended to aid the assessment of a low level of exposure to a mixture, not a high level of exposure. The worked examples were considered to greatly enhance the document.

3.36 A number of further comments were made and the Secretariat undertook to pass the Committee’s comments back to the IPCS.

Horizon scanning

3.37 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 2009 exercise, including those outstanding from the 2008 exercise. From these and Committee members’ own proposals, the COC decided that the following items should be taken forward:

- An update review of the literature on interaction between genotype and chemicals in the environment on the induction of cancer
- A joint meeting with the COM on thresholds of genotoxicity
- Endogenous DNA adducts
- The carcinogenicity of carbon nanotubules
Mononuclear cell leukaemia in the Fischer 344 rat

The cancer risk of exposure to environmental tobacco smoke in childhood

The use of Zebrafish in mechanistic studies

In addition, the Committee asked to discuss the output of a workshop held by the International Life Sciences Institute Health and Environmental Sciences Institute on Intermittent/Short-Term Exposure to Carcinogens to be held in December 2009.

Ongoing topics

Carcinogenicity of mixtures

3.39 The COC continued to discuss the assessment of chemical mixtures with regard to carcinogens and their modes of action. A statement is expected in 2010.

RNA related effects as a mechanism of carcinogenicity

3.40 Ribonucleic acid (RNA), which is made up of nucleic acids, 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.

Functional

3.41 RNA genes in the human genome include transfer RNA (tRNA), ribosomal RNA (rRNA) and various other small non-coding RNAs. Several hundred genes in our genome encode small functional RNA molecules collectively called microRNAs (miRNAs).

3.42 At the 2008 horizon scanning exercise, it was suggested that it would be appropriate to review emerging research data in the scientific literature on RNA related effects as a mechanism of carcinogenicity. The Committee was provided with a review of the role played by mechanisms involving RNA in cancer development. It was decided that the review should be updated to include, if possible, a review of any emerging papers on environmental chemicals interacting with RNA processes. The topic will be discussed further at a future meeting.
The potential carcinogenic risk of Insulin-like growth factor-1 (IGF-1) in the diet

3.43 The COC was asked to advise on concerns raised by a member of the public in relation to a book (“Your Life In Your Hands” by Professor Jane Plant) which suggested that consumption of IGF-1 in dairy produce could lead to an increased risk of developing certain cancers. The Committee considered that the evidence presented in the book was incomplete, and of inconsistent quality, so any conclusions drawn from the book must be regarded as provisional and would need to be confirmed following a fuller systematic review of the scientific literature before they could be acted upon. This is currently ongoing and will be discussed by the Committee in due course.
2009 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

CHAIR

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Professor of Environmental Carcinogenesis, Institute of Cancer Research

MEMBERS

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Non-specialist Member

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SECRETARIAT

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Dr D Benford BSc PhD FBTS  Joint Scientific Secretary – Food Standards Agency

Mr J Battershill BSc MSc  Scientific – Health Protection Agency

Dr L Hetherington BSc PhD  Scientific – Health Protection Agency

Ms S Kennedy  Administrative Secretary– Health Protection Agency
Declaration of COC members interests during the period of this report

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### Force on Guidance for Classification of Carcinogens under GHS

**ILSI HESI, ILSI Europe & ILSI Research Foundation Working Groups on generic risk assessment issues.**

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<td>Professor D Harrison</td>
<td>Renovo Ltd, Manchester UK, INEOA Healthcare, Warrington, UK, Synosia Therapeutics, San Francisco, US</td>
<td>Shareholder, Consultant (no fee payable) Consultant</td>
<td>Medical Research (Scotland) Chair EMMS Nazareth Member Scientific Advisory Committee, Yorkshire Cancer Research Trustee (Healthcare Charity) Trustee</td>
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<tr>
<td>Ms D Howel</td>
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<td>Dr D Lovell</td>
<td>National Grid plc, Pfizer</td>
<td>Shareholder, Shareholder</td>
<td>AstraZeneca National Grid plc, Spouse shareholder</td>
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<tr>
<td>Dr B G Miller</td>
<td>Iberdrola SA</td>
<td>Shareholder</td>
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<tr>
<td>Dr C Powell</td>
<td>GlaxoSmithKline</td>
<td>Shareholder and salary</td>
<td>NONE</td>
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<tr>
<td>Professor R A Roberts</td>
<td>AstraZeneca, HBOS, P &amp; O</td>
<td>Salary, Shareholder, Shareholder</td>
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<tr>
<td>Name</td>
<td>Affiliation</td>
<td>Role</td>
<td>Shareholding</td>
<td>Notes</td>
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<td>Professor D E G Shuker</td>
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<td>(to 31 March 2009)</td>
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<td>Dr P Vineis</td>
<td>NONE</td>
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<td>Dr N Wallis</td>
<td>Pfizer</td>
<td>Salary Shareholder</td>
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<tr>
<td>Dr L Wright (from 1 April 2009)</td>
<td>AstraZeneca</td>
<td>Salary and shareholder</td>
<td>NONE</td>
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