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

LAY SUMMARY

STATEMENT ON THE INTERACTION BETWEEN GENOTYPE AND CHEMICALS IN THE ENVIRONMENT ON THE INDUCTION OF CANCER IN RISK ASSESSMENT

Introduction and Background Information

1. The Committee was asked by the Department of Health to review the available information on the interaction between genotype and exposure to chemicals in the environment and the induction of cancer. The Committee was asked to provide advice on the methods of epidemiological research used in this area and the approaches to identifying genes of interest for such studies. Of particular importance is the evaluation and significance of data from relevant studies in cancer risk assessment.

2. A short summary of the conclusions is given on pages 2 and 3 of this statement. A brief overview of relevant information which will help in understanding the reasons for undertaking this review and conclusions reached is given below and some additional information on the term used is given in the glossary apended to this statement.

- Many diseases (such as cancer) are thought to be due to a combination of heredity and other factors in the environment (such as lifestyle, diet and to a lesser extent exposure to chemicals in the environment). The DNA sequence of an individual (his or her genotype) may be one factor which contributes to whether a person who is exposed to chemical carcinogens (e.g. from tobacco smoke) may develop cancer. (Most chemical carcinogens exert their effects after prolonged exposure, e.g. over several decades)

- The information coming from the Human Genome Project (http://www.ornl.gov/hgmis/project/.html) and the Environmental Genome Project http://www.niehs.nih.gov/envgenom/ is helping scientists to gain an understanding of the differences between people in their DNA sequences (genes) and thus more information about possible chances of getting diseases (such as cancer). These projects are showing that there are a great many small differences between individuals in their DNA sequences.

- There is a lot of knowledge available on how carcinogens can cause cancer (for example how chemicals can be metabolised in the body to form carcinogenic chemicals, see glossary for more information) . It is therefore possible to identify differences in DNA sequences between individuals (for example in genes controlling the metabolism of chemicals) which might affect susceptibility to cancer

- It is already known that a few genes (such as the breast cancer susceptibility gene BraC1) have a very strong association (link) with the occurrence of cancer; in this case breast cancer. However such genes are very rare. It is much more likely that a gene will increase the tendency to develop cancer in a weaker fashion, with a low proportion of carriers actually getting cancer. This review is about whether we can identify any combinations of exposure to chemicals and occurrence of a particular DNA sequence (genotype) that is associated with a higher risk of cancer compared to individuals who may be exposed to the same chemical but do not have the same DNA sequence. [The types of gene concerned (such as those which metabolise chemicals) have, on the available evidence, little or no direct association with cancer.]

Conclusions of Review

3. The Committee reviewed the methods used to investigate possible interactions between genotype, exposure to chemicals and occurrence of cancer. The types of study, which all involved investigating genotype and exposures to chemicals in humans, could be separated into two types. Gene characterisation studies which aim to investigate the nature and strength of interactions. Gene Discovery studies which are intended to screen for genes which might be of importance for future gene characterisations studies.

- There are problems in using the results of many of the available studies because these have investigated too few individuals to allow legitimate conclusions to be made. Scientists/epidemiologists conducting such studies may not have formulated clear reasons for doing the research before conducting the work. These studies often produce a large amount of information and it is possible that some of the associations reported (between genotype and chemical induced cancer) arose by coincidence simply because of the large number of analyses undertaken and could be considered as "chance findings". The Committee felt that the possibility of chance findings was highly likely in the future because such studies would provide information on many hundreds of genes at a time. The Committee felt that investigators should be asked to lodge the reasons for undertaking the research with a third party before the investigations were undertaken so that the possibility of the information being used for purposes that it was never intended could be avoided. This might help to clarify which genes were of most importance in each study.

- The Committee agreed that the most appropriate way to assess the results from many of studies investigating the possible interaction between a particular genotype and exposure to chemicals on the occurrence of cancer should involve the following information. In many cases a provisional assessment would have to be made without full information on number (iii)

    i) Clear information on the mechanisms of carcinogenicity of the chemical under consideration

    ii) An assessment of the strength of the interaction and consistency of the information from epidemiological studies of genotype-environment interaction.

iii) An assessment of the information on the function of the particular gene under consideration.

- The Committee concluded that an assessment of likely numbers of individuals with a particular genotype at risk of developing cancer following exposure to chemicals needed a lot of information before such calculations could be undertaken. This included information on the type and extent of chemical exposure, the numbers of people with genotype in the whole population and in exposed individuals. It would also be necessary to know the incidence of cancer in exposed and non exposed individuals either with or without the particular genotype. It would therefore only be possible to undertake such an assessment in a very few cases given the information currently available.

- The Committee agreed that the available data had so far failed to show any consistent and strong interaction between genotype and chemical induced cancer. It was unlikely that the interactions studied to date (which mainly concerned genes responsible for the metabolism of chemicals) were of importance to public health.

- There is little value in using genetic screening to identify individuals with particular genotypes of interest for carcinogenesis induced by environmental

- However the possibility could not be excluded that important genotype-environment interactions involved in chemically induced cancers would be identified in the future.

- The Committee recommended that it was important to keep this subject under review particularly in the light of expected developments from the Environmental Genome Project based in the U.S.A and other initiatives in this area.

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Glossary of important terms

Association:	The finding that the occurrence of disease and a factor (such as exposure to a chemical) is greater than expected by chance.
Consistency:	The association has been consistently identified in studies using different approaches and by different research groups and in different populations.
Cancer:	A malignant neoplasm (commonly called a tumour) that grows progressively, invades local tissues and spreads to distant sites.
DNA sequence:	The carrier of genetic information for all living organisms except some viruses. Most cells in humans contain 46 chromosomes, each consisting of two strands of DNA which make up genes (see definition given below). Each DNA strand

	consists of two interwound chains of linked nucleotides. The nucleotides are the chemical building blocks of genes.
Environmental Genome Project:	(EGP) was initiated by the US National Institute of Environmental Health Sciences (NIEHS) in 1998.The mission of the EGP is to improve understanding of human genetic susceptibility to environmental exposures. The EGP supports the mission of NIEHS, which includes the goal of understanding how individuals differ in their susceptibility to environmental agents and how these susceptibilities change over time. The EGP has a well developed internet site from where it is possible to obtain a lot of information on the subject of genotype-environment interactions (http://www.niehs.nih.gov/envgenom/home.htm)
Gene:	The functional unit of inheritance: a specific sequence along the DNA, which codes for a product which a specific function in the cell.
Gene characterisation Studies:	Epidemiology studies designed to give information on the nature and strength of interaction between genotype and exposure to chemicals in induction of cancer. There are many different designs which can basically involve either investigation of cases (i.e. individuals who have got cancer) to examine if exposure to chemicals and genotype were risk factors or investigation of large groups of individuals where disease status (i.e. cancer) is unknown. In this instance it may be possible to follow a group of individuals to see who gets cancer or to use records to retrospectively assess the occurrence of cancer within a group. All of these approaches need good information on genotype status of individuals and information on exposures to chemicals.
Gene Discovery Studies:	Studies designed to screen many hundreds (possibly thousands) of genes and particular gene variants to see if there is a potential association with a disease such as cancer. Such studies are becoming feasible due to rapidly advancing methods for sequencing DNA.
Genotype:	The particular DNA sequence seen in an individual.
Genotype Environment Interaction	A biologically relevant effect of two or more factors contributing to the risk (likelihood) of getting a disease (e.g the effect of a particular genotype and exposure to chemicals in the induction of cancer). The degree of interaction can be measured

to examine whether the risk of disease is the sum of the risks associated with individual factors or whether the risk is greater than the sum (e.g a mulitplication of the risks of disease associated with two or more factors)

Human Genome Project (US):

Begun in 1990, the U.S. Human Genome Project is a 13-year effort coordinated by the US Department of Energy and the US National Institutes of Health. The project originally was planned to last 15 years, but effective resource and technological advances have accelerated the expected completion date to 2003. Visit http://www.hgmp.mrc.ac.uk/About/ Project goals are to

- *identify* all the approximately 30,000 genes in human DNA,
- *determine* the sequences of the 3 billion chemical base pairs that make up human DNA,
- *store* this information in databases,
- *improve* tools for data analysis,
- *transfer* related technologies to the private sector, and
- *address* the ethical, legal, and social issues (ELSI) that may arise from the project.

Several types of genome maps have already been completed, and a working draft of the entire human genome sequence was announced in June 2000, with analyses published in February 2001. An important feature of this project is the federal government's long-standing dedication to the transfer of technology to the private sector. By licensing technologies to private companies and awarding grants for innovative research, the project is catalysing the multibillion-dollar U.S. biotechnology industry and fostering the development of new medical applications

Human Genome Mapping Project (U.K)

The UK Human Genome Mapping Project Resource Centre (HGMP-RC) provides access to leading-edge tools for research in the fields of genomics, genetics and functional genomics. The Research Division and the Bioinformatics Division are located on the Hinxton Genome Campus along with the Sanger Centre and the European Bioinformatics Institute.The Biology Services Division of the HGMP-RC is located on the site of the Babraham Institute, Babraham. The Mission of the UK Human Genome Mapping Project are;

- To provide both biological and data resources and services to the medical research community, with a special emphasis on those relevant to the Human Genome Programme.
- To facilitate genomic research by the provision of cost effective centralised collaborative and training facilities.
- To encourage users to share their data, information and resources.

- To encourage the transfer of technology from the academic to commercial/industrial applications.

Mechanisms of chemical carcinogenicity:	There are a wide diversity of mechanisms by which chemicals may cause cancer. However a basic distinction between two types can be made. Chemicals that are mutagenic (in-vivo, i.e in whole animals) are persumed to be potential carcinogens. Other chemicals act by various mechanisms but are not mutagenic (e.g effects on hormones or inducing high levels of irritation/cytotoxicity)
Metabolism of carcinogens:	It has been established that a number of chemicals which are carcinogenic act only after they have been metabolised to chemical structures which are mutagenic. Thus a key step in the carcinogenic mechanism of these chemicals is the metabolism.