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**Burden of Occupational Cancer in
Great Britain**

**Summary Report of Workshop Held on
the 22nd and 23rd November 2004 in
Manchester**

HSL/2005/54

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ABBREVIATIONS

AF	Attributable fraction
CAREX	(European) Carcinogen Exposure Database
CépiDc INSERM	French Epidemiological Center on Medical Cause of Death
CIDI	(HSE) Central Index of Dose Information
CLAW	Control of Lead at Work Regulations (2002)
DALE	Disability-adjusted life expectancy
DALY	Disability-adjusted life years
EH64	HSE summary criteria for occupational exposure limits
EMSU	The Epidemiology & Medical Statistics Unit (HSE)
EPA	(US) Environmental Protection Agency
ESR	Existing Substances Regulations
FINJEM	The Finnish job exposure matrix
FRANCIM	The French Network of Cancer Registries
HPA	Health Protection Agency
HSC	Health and Safety Commission
HSE	Health and Safety Executive
HSL	Health and Safety Laboratory
IARC	International Agency for Research on Cancer
IOM	Institute of Occupational Medicine
ISCO	International Standard Classification of Occupations
ISIC	International Standard Classification of All Economic Activities
JEM	Job exposure matrix
MATGENE	Matrix of Employee Exposures (France)
MbOCA	4,4'-Methylenebis-2-chloroaniline
MDA	4-methylenedioxyamphetamine
NEDB	National Exposure Database
NHL	non-Hodgkin's lymphoma
NIOSH	National Institute for Occupational Safety and Health (USA)
O/E	Observed / expected ratio
OEL	Occupational exposure limit
PAH	Polycyclic aromatic hydrocarbons
PCB	Polychlorinated biphenyl
PE	Population exposed
QALY	Quality-adjusted life years
RR	Relative risk
SME	Small to Medium Sized Enterprises
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
THOR	The Health and Occupation Reporting Network

Executive Summary

HSE's current assessment of the national burden of occupational cancer derives from an estimate of attributable proportion reported by Doll and Peto to the US Congress in 1981, which was based on 1978 cancer mortality data for the USA (Doll and Peto, 1981). Applying that proportion to current cancer mortality rates for Great Britain gives an estimate of 6,000 cancer deaths per year attributable to occupation (uncertainty range 3,000 to 12,000). However, there are doubts about the accuracy of this figure, and it does not provide an adequate basis on which HSE can plan possible workplace intervention strategies.

The aim of this workshop was to assess the methodological approaches and data that might be used to update estimate of the current burden of occupational cancer due to past exposures, and to estimate the future burden as a consequence of recent and current exposures.

The views expressed in this document are an attempt to summarise the discussions held at the workshop and are not necessarily the consensus view of all who were present at the workshop.

The aim of this document is partly to provide some possible research ideas in relation to occupational cancer for HSE, but mainly to inform the work to develop the updated estimate of the current and future number of cancers that might be attributed to occupational causes in Great Britain..

Conclusions:

The workshop participants agreed that it was timely and feasible to update Doll and Peto's 1981 estimate. It was agreed that attention should centre principally on those carcinogenic agents and occupational circumstances (not just chemical exposures) that have been classified by the International Agency for Research on Cancer as known or probable carcinogens, and that have occurred in British workplaces in recent decades. However, the possible impact of other unrecognised occupational carcinogens should not be ignored in the overall assessment. It was acknowledged that some exposures which no longer occur in the workplace may be relevant to the current burden of occupational cancer, although not to that in the future. It was agreed that most of the major occupational carcinogens have probably been identified, but it was acknowledged that for newer occupational exposures, follow-up time has been insufficient for a full evaluation of human carcinogenicity.

In determining which agents and occupational circumstances should be looked at in more detail, it will be important to define explicit criteria. Account must be taken of levels and durations of exposure (not just the numbers exposed), and how these have changed over time. As well as analyses based on well-established occupational carcinogens, upper limits for attributable numbers should be estimated, taking account of occupational groups with consistently elevated rates of cancer that could plausibly reflect workplace hazards. It was agreed that most of the excess of cancer attributable to occupation is likely to occur in the larger number of workers with relatively low exposures (rather than the minority with high exposures), and that direct assessment of the risks associated with those low exposure scenarios may not always be possible through standard epidemiological methods. Thus, extrapolation and other indirect approaches may be required. However, it would be reasonable to ignore occupational hazards that are unlikely to contribute more than two new cancers per year in the country as a whole.

The workshop identified various approaches that could be used to assess the numbers of cancers attributable to occupational exposures, including direct estimation from population-based case-control studies, and collation of data on exposure-response from one source with information about the national frequency and distribution of exposures from another. The optimal method will differ by cancer and carcinogen.

Where needed, information on exposure-response relationships should be obtained through systematic review of the relevant scientific literature. Ideally, it would come from studies in Great Britain, but relevant data from other countries will also need to be considered.

FINJEM, modified to Great Britain would be a useful tool in estimating the numbers of workers exposed to relevant agents, as would data from UK censuses on the national distribution of occupations and industries. For information on levels of exposure, reliance will have to be placed on readily available data, such as from NEDB, industry and the published scientific literature. A mean exposure might be all that is required if a linear dose-response relationship can be assumed. Otherwise, the distribution of exposures across a range of categories will be needed.

Final results should be presented with ranges of uncertainty that take account of potential bias and confounding issues, as well as chance variation and doubts relating to missing data. Consideration should be given to estimating impacts on disability-adjusted life-years (DALYs) as well as attributable numbers of cancers.

The ultimate goal should not be forgotten in that, as well as updating estimates of the overall burden of occupational cancer, HSE is looking (to the extent that the available data will allow) for a break-down by cancer and carcinogen that could be used to identify and prioritise possible workplace interventions aimed at reducing the future risk of occupational cancer.

1.0 Introduction:

In 1981 in their report to the US Congress, Doll and Peto presented a method of estimating the approximate current effects of occupation on cancer mortality in the US (Doll & Peto, 1981). The proportion of cancer they tentatively attributed to occupation was about 4% of all US cancer deaths. Although not a precise estimate, Doll and Peto believed that their estimate was unlikely to be out by more than a factor of about two. Thus an uncertainty range associated with the 4% estimate was 2% to 8%. Applying these proportions to current mortality in Great Britain (GB) leads to an estimate of around 6000 cancer deaths (uncertainty range 3000 to 12000) currently occurring each year in GB as a result of occupational exposures. Given that the estimate on which these figures are based, and the methodology used are nearly 25 years old, it is appropriate that its validity today be reassessed.

By far the largest contribution to the estimated 4% cancers was from lung cancer (~ 2/3rds of the total). Doll and Peto suggested that the most appropriate way to improve this estimate was to conduct a nationally representative case-control study of lung cancer. This would allow adjustment for all other relevant factors including non-work factors particularly smoking. However, conducting such a study in GB would be prohibitively expensive (costing at least several million pounds). To address this problem HSE have funded new work to review the methods and data required to re-evaluate the 'attributable' fraction of occupational cancer in GB. This work forms an important component of HSE's 'Disease Reduction Programme', which covers occupational illness caused by chemicals, including the contribution of carcinogens. One objective for this programme is to look ahead from current exposures to anticipate the future disease burden for conditions which arise after a long period of latency, which is typical for most chemically induced cancers. The objective of the 'Disease Reduction Programme' is to deliver public sector target reductions in the incidence of ill health related to chemicals. In the case of human cancers, for which the period between exposure and disease may be years to decades, it is not expected that significant reductions in the incidence of cancers will be achieved by 2010. However, it is important that HSE develops a strategy to identify interventions that are effective in reducing the disease burden in the long term. Consequently a targeted strategy will be required to ensure that by 2010 there is at least evidence of improved controls and reduced exposure to carcinogens in the workplace. This strategy will be based upon a systematic review of current carcinogen exposures in UK workplaces, as well as an expert evaluation of the most appropriate statistical and epidemiological tools, it will make use of the available data on carcinogenic exposures. The aim of this current review exercise is to assess the current and future attributable burden of occupational cancers in GB.

1.1 Background: It should be noted that not all occupational carcinogens are necessarily chemical agents or directly related to a particular chemical. For example, the Health Protection Agency (HPA) have estimated that incidental exposure to radon in the workplace causes approximately 250 lung cancers per year in Great Britain (Dixon DW personal communication). Researchers from Imperial College London (Jamrozik 2005) have estimated that in 2003 approximately 600 deaths occurred each year in people aged under 65 (from a combination of lung cancer, heart disease and stroke) as a result of occupational exposure to environmental tobacco smoke. An estimated 160 of these 600 deaths were due to lung cancer. More cases were reported to occur amongst those aged over 65. The Health and Occupation Reporting Network (THOR) surveillance scheme estimates that 360 occupational skin cancers occur each year and most are due to occupational exposure to sunlight (www.hse.gov.uk/statistics/causdis/sources.htm). This could be an underestimate due to the voluntary nature of the reporting through the THOR scheme, although there could also be a tendency to overestimate the number because of inappropriate attribution in individual cases.

There is no consensus amongst relevant experts about the current burden of occupational cancer in GB. The previous Doll and Peto estimate was based on mortality data and would not therefore include the growing proportion of cancers that are not always fatal (e.g., breast cancer and leukaemia). To provide an updated estimate of current cancer burden would therefore need estimates of the number of incident cancers and not just the fatal cancers. Another complicating factor is the potential long time (perhaps 20-30 years) between exposure to carcinogens and the appearance of cancer. In some instances (e.g. mesothelioma) this delay can be much longer. Currently mortality rates generally

reflect occupational exposures from two to three decades ago. Therefore it is important that any attempt to update the Doll and Peto exercise includes an estimate of the number of future cancers that might occur as a result of current exposures to carcinogens. It is important that any output from the current workshops and re-analysis of the occupational cancer data allows HSE to determine the number of cancers that might be preventable in the future as a result of appropriate interventions.

1.2 HSE Epidemiological Study of Occupational Cancer: The aim of these workshops and review exercise is to provide HSE with:

- A practical and reasonably robust method for estimating the number of cases of cancers caused by workplace exposures.
- Current and predicted estimates of the number of occupational cancers.
- Recommendations for areas where HSE should prioritise efforts to reduce the incidence of occupational cancer.
- An assessment of the relative importance of occupational cancer compared with other occupational illnesses.

These outputs will be developed during two workshops and by commissioning a team of epidemiologists and statisticians (using appropriate occupational hygiene and toxicological advice as required), to determine the current and future attributable fraction of occupational cancers in GB.

The first of these workshops was held on the 23rd & 24th November 2004. International and national experts in epidemiology, cancer and occupational hygiene attended the meeting (see Appendix A for participant list). In the first part of the meeting the experts were asked to recommend which carcinogens and cancer sites should be prioritised when calculating the attributable risk for GB. In the second half of the meeting they were asked to consider the most appropriate statistical and epidemiological methods to determine the attributable risk for those carcinogen/cancer combinations.

The second stage of the work will involve a review of the current attributable risk for occupational carcinogens using a prioritised list of agents and cancer sites. A provisional estimate of current attributable risk will first be calculated using risk estimates from key research papers and provisional prevalence figures. The team will then employ more complex methods (where the data allow) to determine the current burden, as well as reviewing methods that may be suitable for assessing future burden of the disease. These results will be presented and discussed at the second workshop to be held in Spring 2006. Additional outputs from the second workshop will include:

- An indication of the relative burden of cancer compared to other occupational ill-health endpoints.
- Identification of any shortcomings in methodology and data for estimating the occupational cancer burden in GB.

The results from the analysis of the occupational cancer data together with the conclusions formed at the final workshop will be submitted to a peer-reviewed scientific journal (Occupational and Environmental Medicine).

This interim report is a summary of the first meeting and represents work in progress with technical discussions about choice of optimal methodology. Therefore this summary will focus mostly on those aspects of the meeting that are of general interest to stakeholders of the carcinogens component of the HSE Disease Reduction Programme.

2.0 Summary of the Meeting Proceedings

The meeting was organised over two days and consisted of presentations and ‘break out’ discussion groups. The invited experts were asked to provide an overview of relevant studies of occupational cancer burden or to focus on methods and data that had been used to determine the attributable fraction of cancer due to occupational causes. On day one of the meeting the participants were divided into 4 groups and asked to review the case for including IARC Class 1 and 2A carcinogens in a prioritised list of agents. Each group was asked to consider the major carcinogens for particular organs and to identify agents which had not previously been considered or which represented a potential emerging problem for the future burden of cancer. The findings of each group were then presented in a general discussion section in which the criteria for inclusion (or exclusion) of particular agents were argued. On the second day of the meeting these groups were asked to consider the major agents previously identified and to identify relevant sources of data on occupational exposure (relevant to GB), disease incidence and toxicology, and possible methodologies for determining the attributable cancer risk for these particular agents. A full transcription of these discussions has been prepared and is available on request from the Health Effects Section of the Health & Safety Laboratory.

This report is a thematic summary of these talks and presentations.

2.1 The HSC/HSE Strategy for Occupational Cancer:

Steve Coldrick (Director of the Disease Reduction Programme; HSE) outlined the Health & Safety Commission (HSC) strategy for delivering the government public sector targets on reducing the incidence rate of occupational ill health by 2010. HSE recognised that these targets cannot be achieved, without developing closer partnerships with other stakeholders in government, academia, and industry. To achieve these targets HSE would have to focus on its core business and develop an intervention strategy that was best placed to reduce workplace injuries and ill health. HSC has set out a vision that “Health & Safety in the workplace should be the cornerstone of a civilised society”. To ensure delivery of this objective, programmes of work have been organised to ensure effective communication and partnership with other organisations. Occupational cancer had been placed under the Disease Reduction Programme.

The scope of this programme also encompasses respiratory and skin diseases. The focus of the programme is to identify activities that best address the desired outcome to reduce the rate of occupational illness, and it therefore concentrates on risk management, education, intervention, and human behavior. It was recognised that for occupational cancers none of these activities could bring about a reduction in the incidence of occupational cancers by 2010. Therefore different interim (proxy) measures will be used to demonstrate that a successful strategy is being adopted. It was recognised that there was a need for an up-to-date review of the burden of occupational cancers as well as of methods to determine current and future burdens.

There is also a need to develop a good evidence base to improve knowledge by involving the best science (the purpose behind this workshop), and involving the wider community of experts to achieve consensus on the main priorities. It is intended that this would lead to effective strategies for intervention work, based upon pilot investigations with an evaluation of the outcomes. From the HSE perspective it was very important that the objectives of this project be practically implemented, and that there be agreement about the methodology and data requirements. HSE regards this work as a core component of its strategy for work on occupational carcinogens.

2.2 Background Studies of Attributable Risk for Occupational Cancers

2.2.1 Progress Since Doll and Peto: Dr Lesley Rushton presented an overview of studies since the seminal work by Doll and Peto. In this she addressed the questions of why it was necessary to measure the cancer burden, what the burden meant, and how best to meet the challenges posed by measuring

the burden. The key reasons for determining the burden were to identify the major risk factors and high-risk populations, to provide 'performance' indicators for monitoring the success of intervention programs and to support decisions for priority actions and risk reduction. This process could also facilitate planning for future needs and foster priority setting in health research.

Doll and Peto (1981) defined the 'attributable' risk as the percentage of cancers that "might be avoidable" in various ways or groups of ways. However, any interventions would need to be socially acceptable now and in the future, although it is not easy to allow for unforeseen advances in basic scientific research. For example, since the estimates were made in 1981 by Doll and Peto there have been tremendous advances in our knowledge of the causes and mechanisms of cancer. To develop a successful avoidance strategy needs an understanding of causality, and in particular the relationship between exposure and onset of carcinogenesis. The strength, consistency and plausibility of any association, needs therefore to be evaluated. Avoidability has often been measured using the attributable (excess) fraction, which is calculated as a function of both the relative risk and the proportion of those exposed to the risk factor. Reducing either of these reduces the attributable fraction. Epidemiological and experimental studies have provided evidence that cancer is preventable.

Doll & Peto (1981) had classified the occupational causation of cancers as either not known, possible, or almost certain. For those cancers considered as possibly caused by occupation (without definite evidence) they assumed that a small proportion of cases (1% for males and 0.5% for female) were attributed to occupational exposure. For the cancers that were considered 'certainly caused' by occupation they reviewed epidemiological studies and used expert judgment to obtain an estimate of the proportion of cancers caused by occupational exposure. Based upon this method they estimated the proportion of all cancers that were attributable to occupational exposure as ~4% (with an uncertainty range from 2-8%). Since the Doll and Peto study (1981) several other methods have been developed to estimate the global burden of occupational disease.

One approach to estimating the total burden of occupational cancer in individual countries has focused on occupations, and applied national cancer rates for specific occupations for countries closest in geography (or economic development) to nations with no occupation-specific cancer data. A second approach has focused on diseases and compared age/sex/occupation incidence rates for specific diseases from one country to another. Thirdly, an occupational exposure driven approach can be used to identify the number of people exposed to specific carcinogens and estimate the proportion of cases due to these exposures. The data could also be used to estimate the social and economic impact of the disease by calculating summary measures such as disability-adjusted life years (DALY), quality-adjusted life years (QALY) and disability-adjusted life expectancy (DALE).

For HSE, the challenges are likely to be encountered in relation to the adequacy of data, i.e., its coverage, accuracy, and relevance. It needs to be decided how best to determine previous and current exposures, how to deal with multiple occupational and non-occupational causes (or confounding issues); co-morbidity; and the impact of any interventions on diseases which have long latency.

Points for Consideration / Actions by HSE

- To deliver this review of occupational cancer burden HSE may face challenges in relation to the adequacy of the data that it holds on exposure as well as those exposed in the workplace;
- The key factors that will need to be considered are the coverage, accuracy, and relevance of the data for this current and future reviews of the burden of disease;
- HSE needs to develop effective strategies to determine previous and current exposures as well as multiple occupational and non-occupational causes (or confounding issues);
- In the light of this analysis HSE needs to better understand co-morbidity factors and how any intervention they design will impact on diseases that have a long latency period.

2.2.2 Cancer Risk Attributable To Occupation in Finland: Eero Pukkala outlined a national strategy that had been adopted in Finland to collect data on the entire population of working age and how this comprehensive data set had been used in the early 1990s to calculate the attributable fraction related to occupational exposure (Pukkala, 1995). The core resource was based around precise and effective registers that linked occupational categories from the 1970 population census with national cancer registry data. The observed numbers of cancer cases in 1971-1985 were then calculated for 311 occupational categories and compared with the expected numbers based on incidence rates among the entire active population of the same social class.

The excess number of occupationally related cancers was calculated and it was determined that 0.8% of all cancer cases among men and 0.7% among women were related to occupational causes. However, if an O/E ratio of 1.2 was used, the respective proportion of cancers attributable to occupational exposure was 5.5% in men and 4.7% in women. This study revealed similar results to those obtained by specialist evaluation following extensive reviews of published studies. The relative fractions of occupation-related excesses among males were largest (about 30%) for rare cancers of the pharynx and renal pelvis. The absolute numbers of excess cases were largest for cancer of the lung, kidney, lip, colon and bladder. Among women the highest percentages attributable to occupation were for cancers of the lip, vagina and soft tissue, and small cell and squamous cell carcinoma of the lung. The absolute numbers of excess cases were largest for cancers of the breast, lung and female genital organs. Social class (and related health behaviour) was strongly associated with occupation. If cancer incidence in the social class with lowest incidence rate was set as a target level, and cancer incidences above this level considered as excessive, about one-fifth of all cases were attributable to social class, pointing indirectly to differences in occupationally related behaviour. Socio-economic status (SES) variation in cancer patient survival (Auvinen *et al*, 1995) causes discrepancy between estimates based on cancer mortality and cancer incidence. This is because the majority of workers in occupations that have traditionally had the highest occupational exposures belong to lower SES. Therefore they die from similar cancers more often than less exposed persons, and consequently estimates of work-related risk may overestimate the true risk.

The Finnish job exposure matrix (FINJEM) allows census-based occupational estimates of cumulative exposure to chemicals and other work-related carcinogens and the changes in exposure levels during the post-war decades. It is possible to calculate dose-specific relative risks, and to determine factors to adjust for confounding influences not directly related to work such as smoking. More specific estimates of the population attributable fraction related to specific agents and work processes can be determined. A newly published study (Pukkala *et al*, 2005) has indicated that this 'all-population' register replicates dose-response risk estimates derived from specific smaller studies.

These occupation-cancer databases have been extended to include more information for more recent years and data from other Nordic countries (Andersen *et al*, 1999). An ongoing project will link the occupation-specific O/E numbers of incident cancer cases from a period of 43 years, about 4 million cancer cases) to likelihoods and levels of exposure to occupational carcinogens in all five Nordic countries and produce whole-population dose-response estimates for all relevant cancer sites (<http://www.cancerregistry.fi/eng/research/10-40-159.html>). In addition to the features utilised in the earlier publications, the Nordic national JEMs will separate the exposure estimates for men and women, and also pay attention to the modern non-chemical occupational hazards such as lack of physical exercise that is estimated to cause more work-related cancer than all traditional carcinogens combined.

Points for Consideration / Actions by HSE

- In Finland the comprehensive collection of data on carcinogenic exposures, exposure to confounding factors, disease incidence and other demographic information has helped to identify the major occupational cancers amongst males and females as well as highlighting the potential impact of socioeconomic status on risk of developing cancer.
- In GB, the data held on occupational carcinogens largely reflect exposure of male workers. HSE needs to consider how it can assess those agents that present the highest risk for development of female cancers. This may require an assessment of the data collected under FINJEM (or from other European economies for which comprehensive data has been collected) to identify categories of exposure for which targeted intervention could be developed.
- FINJEM and the methodology to calculate dose-response patterns for work related risk factors in entire populations have been successfully modified for several European countries. It is likely that this could also be done for GB.
- HSE needs to consider the relationship between socioeconomic status and the risk of occupational cancer particularly with respect to likely confounding factors.

2.2.3: Occupational Attributable Fraction Estimation in France: Marcel Goldberg outlined the objectives that had been set by the Department of Occupational Health of the National Institute for Health in France. The aim of the program was to develop health surveillance for occupationally attributable diseases. This involved estimation of the fraction and number of diseases and/or deaths attributable to occupation in the general population in France. As there is an established system of compensation for workers with some occupational illnesses an attempt was made to compare the number compensated for occupational related diseases with the estimated attributable fractions derived from exposure and surveillance data.

The first stage in this process was to estimate the fraction and number of cancers attributable to occupational exposure. Attributable fraction estimates were first collected from published studies based in France in which the incidence and mortality data for these diseases had been collected. Compensation arrangements are made for the five main cancers of lung; pleural mesothelioma; bladder; leukemia; and nasal sinus. The estimates of the attributable fractions for these cancers were obtained from studies published in France, Finland, Sweden, other parts of Europe and the USA. The incidence of cancer was estimated using FRANCIM and the cancer mortality data were obtained from CépiDc INSERM.

The number of compensated cases for males in 1999 was as follows; mesothelioma (310); lung (458); bladder (7); leukemia (27); nasal sinus (67). To derive the attributable fraction for these cancers, occupational data at the general population level were used along with job exposure matrices for IARC Group 1 carcinogens (established human carcinogens) to estimate the lifelong prevalence of exposure in the French population. The attributable numbers were also derived from national incidence/mortality data, and the calculated fractions were compared to the numbers of cases compensated for their cancer. The study sample was derived from subjects extracted from 15 French population-based case-control studies (from 1984 to 2003) for which there was a full history of occupation, exposure, and type of industry (ISCO-ISIC codes), along with the subjects characteristics such as date of birth, gender, etc. The sample was checked as representative of the French male population and consisted of 7,878 males with a total of 300,690 job-years. The data on exposure history were derived from the MATGENE project in which a series of population-based job exposure matrices (JEMs) were applied based upon indices for the probability, intensity, frequency, and peak, exposures.

The analysis of these data was carried out by several means. In the first case this was done by establishing the annual cumulative exposure for every subject in the sample from the JEM data. The expected number of deaths in the absence of exposure (NO) was based on the assumption that this

sample was a representative cohort to which the general population 'age specific' mortality rates applied. To calculate the expected additional mortality in the sample due to exposure, the general population age specific mortality rates were multiplied by the relative risks applied year by year to 'person-years' of the subjects previously exposed (N1). The expected attributable number (AN=[N1-N0]) and attributable fraction of deaths (AF=[N1-N0] / N1) were then determined.

An alternative method was based upon Levin's formula ($AF = P(e) [RR-1] / [1-P(e)[RR-1]]$), where P(e) is the proportion of the population exposed (Levin, 1973). This method does not use the general population rates for mortality and can only be used with categorical exposure risk relationships. In this study the analysis was stratified by age. The cumulative exposure and proportion of person-years with 'null' cumulative exposure for each 5 years age class was then used to derive the value of PE. The 'attributable' fraction estimates for each age class were then used to derive the global attributable numbers and fractions. When applied to data for asbestos and lung cancers the attributable fractions estimated using a relative risk of 1.5 (for both methods) gave similar estimates of the proportion of occupational cases (16.1% vs. 15.4% for Levin's method). Thus of 19,600 observed lung cancers in the French male population, 3,020-3,150 were attributable to occupational exposure. Increasing the relative risk to 2.3 essentially doubled the attributable proportion of cases whichever method was used to determine this. These methods were also applied to wood dust and nasal cancer where the relative risk is high (~10) resulting in ~196 of a total 420 cases being attributed to occupational exposure.

These estimates of attributable cancers for asbestos and lung cancer, and wood dust and nasal cancer were respectively 10 fold and 3 fold higher than the number of cases compensated for these cancers during this period. With regard to the expected additional mortality estimates it was necessary to consider the sample population as a cohort, and assume that there was a linear relationship between exposure and risk. Future work will include development of the MATGENE project, extending the job exposure matrix data for other IARC Class 1 carcinogens and updating the population sample to include women.

Points for Consideration / Actions by HSE

- To identify relevant studies and data regarding occupational exposure to carcinogens HSE should consider whether there is value in developing partnerships with other European countries to share this information.

2.2.4: Estimating the Future Burden of Mesothelioma Mortality in Great Britain and The Proportion of Lung Cancers Attributable to Asbestos: In this presentation John Hodgson and Andy Darnton (EMSU) summarised the ongoing evaluation of asbestos associated mesothelioma and other lung cancers. Asbestos is an unusual occupational carcinogen, and mesothelioma (the main disease that results from exposure) has not been recognised as having any other important risk factor. The disease once diagnosed is rapidly fatal and the annual incidence can be well approximated by use of the mortality numbers. This has enabled two recent analyses to be carried out by HSE statisticians. In the first analysis detailed mesothelioma mortality data were used to predict future numbers of deaths from asbestos exposure. In the second study the relative mesothelioma mortality amongst occupational groups was used as an index of asbestos exposure (along with information about smoking habits) to model lung cancer mortality and to estimate the number of asbestos-related lung cancers in Great Britain.

A study published in 1995 (Peto J, *et al* 1995) employed a simple birth cohort model to assess the increase in cases of mesothelioma and this suggested a peak of 2700 to 3300 deaths around the year 2020. However the data only conformed to the model up to 1991 and then departed from the predicted pattern thereafter. Consequently a new modelling approach was adopted (based on the Health Effects Institute/Peto risk model) in which: (1) risk is assumed to be proportional to years since first exposure lagged by 10 years raised to a power, k, between 3 and 4; (2) the effects of successive years exposure are additive; and (3) individual exposure is adequately approximated by the product of two factors,

one defined by year, the other by age (Hodgson *et al*, 2005). The model also allowed for the clearance of asbestos from lung and for a trend in the completeness of mesothelioma diagnosis. The exposure pattern implied by this model reduced rapidly after a peak in the mid 1960s, but the estimates become increasingly uncertain, and effectively the value of the extrapolated data from the early 1980s onwards is undetermined.

Within this model, the values of k and of h (the "half life" for clearance of asbestos from the lung) are highly correlated and cannot be separately estimated. The question of whether a clearance factor should be assumed was addressed by looking at two variants of the basic model. One model assumed no clearance of asbestos from the lung and the other assumed clearance with a half-life of 15 years. The adequacy of these models was examined in terms of the residual deviance from the predicted versus observed fitted deaths. In terms of overall statistical fit, there was very little to choose between these models. However, one key difference (apart from the distinction between clearance and non clearance) between the models was the implied time path for exposure of the population to asbestos. The profiles were similar up to the 1950s but thereafter deviated. To assess which was the best model, comparisons were made between the actual patterns of asbestos imports and the implied exposure pattern, taking into account differences between types of asbestos fibre. This suggested, on balance, that the non-clearance model could be preferred.

In the second study the number of asbestos related lung cancer deaths in GB over the period 1980-2000 was estimated by modelling overall lung cancer mortality across occupational groups in terms of asbestos exposure, smoking habits and occupation type (as a proxy for socio-economic factors). Proportional mortality ratios (PMRs) for lung cancer and mesothelioma for the 20-year period 1980-2000 (excluding 1981) were calculated for occupational groups and smoking indicators were developed from three general household surveys carried out during the 1980s and 1990s. The mesothelioma PMRs were used as an index of asbestos exposure among occupational groups.

The fitted Poisson regression model included variables for type of occupation, asbestos exposure index, the proportion of current cigarette smokers, the average age started smoking, the proportion of ex-smokers, and the average quantity of cigarettes smoked per day. Since type of occupation may itself be related to asbestos exposure, an alternative model without this factor was also fitted. In order to calculate the number of asbestos related lung cancers using each of the two models, the predicted number of lung cancer deaths for 'no asbestos exposure' were calculated for each occupation. This was then subtracted from the actual fitted values for each occupation. Summing over all the occupations then gave an estimate of the total number of asbestos related lung cancers for occupation and this was then scaled up to represent the whole of male population for the analysis period. Of the 211 occupations, 131 were included in the analysis and together these accounted for 91% of the total number of male lung cancer deaths that had valid occupational codes and 94% of the male mesothelioma deaths.

In both models the effect of the asbestos exposure index was small in comparison to the type of occupation and smoking variables. The ratio of asbestos-related lung cancer deaths to mesothelioma deaths in the period was estimated to be between 0.75 and 1.0. This is equivalent to between 11,500 to 16,500 male deaths (or 2-3% of the total male lung cancer deaths) in Great Britain attributable to asbestos exposure during the study period. The caveats with this study arose from difficulties in directly relating the model to physical exposure measurements; death certificates only recording the decedents' last occupations; other risk factors for lung cancer not being explicitly included; and no account being taken of trends in mortality or smoking over time. Hence there are difficulties in applying the model to future trends.

Points for Consideration / Actions by HSE:

- HSE needs to consider the impact of occupation and confounding factors such as smoking when developing interventions even for those carcinogens such as asbestos where we hold more comprehensive sets of data.
- Restricting the input data, for example to the pre-1990 period, and then checking the model predictions for later years against the known outcome should test the robustness of the prediction model.

2.2.5 Listing Occupational Carcinogens: Paolo Boffetta reviewed the methods that have been employed by IARC to classify carcinogens and emphasised that many human cancers are caused by occupational carcinogens. There is a large volume of epidemiological and experimental data concerning cancer risks in different work environments. The IARC listing, however, has not taken potency into consideration, and contains inconsistent information about occupation; the industry in which the substances is used; and the type of cancer associated with this exposure.

The International Agency for Research on Cancer has used this large volume of data (augmented with additional information), to draw together a more systematic classification of occupational carcinogens, the industries in which they are found, and the target organs. Within the occupational setting, 28 agents were recognised as definite carcinogens, 27 agents as probable carcinogens, and 113 agents as possible carcinogens. For the definite Class 1 human carcinogens the major target organs, apart from lung and bladder, are breast; bone; haematopoietic cancers (related to ionising radiation); and mesothelial cancers (related to asbestos and other mineral / organic fibres). For many of these cancers exposure to tobacco smoke is a major confounding factor. Whilst the number of class 1 agents has remained largely unchanged during the last 10 years there have been changes to some type 2B agents with some being reclassified as 2A agents.

The occupations and industries where there is significant exposure to Class 1 major carcinogens include metalworking; fuel and solvent processing; the leather and rubber industries; the dye industry and woodworking. The group of probable occupational carcinogens includes polycyclic aromatic hydrocarbons; fossil fuel products; intermediaries in plastic manufacture; chlorinated hydrocarbons; pesticides and aromatic amines. The major target organs for these agents include the lung; bladder; kidney; cervix, and haematopoietic tissue. The industries where exposures to Class 2A may occur include artistic glass manufacture; hairdressing; cobalt manufacture; and petroleum refining. The Class 2B 'possible' human occupational carcinogens include refractory ceramic fibres; welding fumes; nickel alloys; petroleum combustion products; solvents; and some pesticides.

In the discussion following Paulo Boffeta's talk, the question was raised about other important causes of occupational cancer in GB that might have been overlooked. Dr Boffetta considered that the issue of stress and shift work should be considered as possibly important factors, particularly for female workers and the risk of developing breast cancer. Another area of growing concern was gallium arsenide exposure in semiconductor manufacture. There is wide spread exposure to smoke carcinogens both from environmental tobacco smoke and combustion of fossil fuels, diesel fuels, and combustion of rubbish and waste. The growing importance of these sources of exposure was recognised by the reclassification of diesel emission as a class 2A carcinogen.

Points for Consideration / Actions by HSE

- To compile a priority list of human occupational carcinogens, with the focus of this work devoted to IARC Class 1 and 2A agents.
- Most class 2B agents are characterised by their carcinogenic activity in animal models. Only if there is evidence of potential human carcinogenicity should these agents be considered for inclusion in this exercise.
- Where there are uncertainties (e.g., the role of stress) but insufficient data, HSE should consider focused research to reduce the uncertainties.
- If shift work is an additional risk factor then this may be moderated by lifestyle factors. This raises the question, can HSE impact on these factors using an intervention strategy?
- If there is a contribution to cancer from physical inactivity, does this fall within the responsibility of HSE or the Department of Health?
- Lifestyle factors, stress, diet, and smoking may all impact directly or indirectly as cofactors increasing the risk of cancers developing from occupational exposures. How will HSE intervene in terms of major risk factors (such as carcinogens) and at the same time deal with these contributory factors?
- Some exposures may be amenable to regulatory control but many of these other factors are more relevant to public health policy and to other government departments. Does HSE intend to restrict itself to those factors for which it can bring about change within the workplace?
- The pattern of exposure to some carcinogens may be changing significantly with time. For example, vinyl chloride exposure around waste disposal sites may have increased. How can HSE maintain its understanding of the impact of these changes on present and future populations of workers?

2.3 Review of Sources of Data and Methodology To Estimate Current and Future Attributable Risk for Occupational Carcinogens

2.3.1 Estimating Exposure to Carcinogens in Great Britain: In this review John Cherrie discussed the different exposure databases and methods that could be used to assess the historical and sector exposures to occupational carcinogens. The exposure to hazardous agents may vary in time due to changing use, control measures, working practices, or differences within and between businesses and between different countries. No uniform monitoring systems have been employed in Great Britain to track changes in the use and exposure to most occupational hazards and this includes carcinogens. Consequently, it is necessary to use different sources of data to review the cancers attributable to occupational causes and there are methodological assumptions behind the use of these sources of data.

In this review, carcinogenic agents (or work circumstances) were identified from IARC class 1 and 2A lists. Exposure prevalence estimates for 1990/93 were obtained from the CARcinogen EXposure or CAREX database (Kauppinen *et al*, 2000). For those situations not covered by CAREX, the prevalence of exposure was estimated for four carcinogenic exposure circumstances. This resulted in a list of 64 agents/circumstances with ~7 million people in GB occupationally exposed to these agents.

The first ten agents (and processes) made up 83% of the estimated total number of people exposed to carcinogens and included passive exposure to tobacco smoke and exposure to solar radiation. The other major factors include crystalline silica; radon; diesel exhaust; wood dust; benzene; ethylene dibromide; inorganic lead compounds; and chemicals used in hairdressing.

The next 10 agents/processes included decorating paints; chromium VI compounds; tetrachloroethylene; coal tar products; iron and steel foundries; asbestos; formaldehyde; nickel compounds; acid mists; and cadmium containing compounds. Together with the top ten agents this additional group accounted for 97% of those exposed occupationally to identified carcinogens.

Consequently the last ten agents (processes) added very little to this total. The agents included cobalt metal; arsenic; X-rays and gamma rays; styrene; trichloroethylene; rubber and beryllium compounds; cyclophosphamide; cisplatin and vinyl chloride. Together all 30 agents accounted for 99.5% of those occupationally exposed to IARC Class 1 and 2A carcinogens in Great Britain.

This review demonstrated problems with the use of the CAREX estimates for some of these agents for Great Britain. When compared to HSE estimates for 16 of these agents, the estimated number of those exposed was lower than the estimates derived from CAREX. However, for radiation the HSE data suggested more were exposed (approximately 250,000) compared to the CAREX data (approximately 15,000). These differences may be due to different thresholds for inclusion of people as 'exposed' or 'non-exposed'. There were other examples where it was clear that the CAREX data were unrepresentative of the situation in Great Britain, but in general the ranking of these agents using CAREX data seemed broadly compatible with the expected estimates of the numbers exposed for Great Britain. It is also likely that the CAREX data do not properly reflect the historical prevalence of exposures in GB, but some information should be available from HSE and other sources for some of these agents. Despite these limitations it was concluded that the CAREX database was the best starting point for estimating exposure prevalence.

In terms of which agents could be excluded from the list, some of the last ten agents (exposure circumstances) could be removed on the basis of being 'unproven' carcinogens or 'unlikely' exposure risks with the exception of three that require further consideration. These are therapeutic anti-neoplastic drugs for which ~4 million prescriptions are dispensed in the GB each year, and exposure to rubber constituents and trichloroethylene. The numbers of people exposed over time should be considered carefully because there have been significant changes in the numbers employed (and potentially exposed) in key industries. For example, from the 1950's onwards there have been big reductions in the numbers working in the iron and steel industry and more gradual reductions in the leather and coking industries. The data for ionising radiation taken from HSE's Central Index of Dose Information CIDI also showed a decline in numbers of people exposed.

Another source of information on exposure to these agents is the HSE National Exposure Database (NEDB) for which data are available for most identified substances. In addition, there are data published in peer reviewed papers and surveys and reports compiled by the Health and Safety Laboratory (HSL). Large amounts of data have been gathered by some sectors of industry on benzene and coke oven emissions. Unfortunately there are no systematic data for environmental tobacco smoke exposure or sunlight. At least 20 of these substances were identified in the NEDB database with the largest number of samples collected for crystalline silica; asbestos; chromium VI compounds; cobalt; rubber dust/fumes; and wood dust.

The year-on-year measurement of some of these agents has demonstrated reductions in the mean exposure over the last 20 years, e.g., crystalline silica. Furthermore when the mean exposure level was set as a ratio of the specific occupational limit (OEL), almost half of the agents e.g., arsenic, sulphuric acid, and tungsten, demonstrated evidence of control beneath the limit. For beryllium, most measurements were below the detection limit, although the exposure limit is set very low for this metal. Other agents showed poorer control and these included asbestos; benzene; chromium VI compounds; lead; and wood dust.

Exposure to rubber dust was more difficult to assess. An evaluation of reductions in exposure with time, which included data from other European countries, showed exposures substantially higher in Germany and Poland compared to GB and Sweden. However, in all countries there was an average eight-fold reduction in exposures from the 1970s to 2004. Toluene exposure data taken from NEDB showed an annual 6% decrease over time but with substantial variation between industries. Wood dust (hard and softwood) exposure was also taken from NEDB and showed a lot of variability with an ~2 fold reduction in exposure from the mid 1980s to the present. For exposure to coking fumes (comparing GB and the USA) there was a sharp reduction in exposure in the USA after the 1970's but just a steady less dramatic decrease in GB. Again closer examination of the data showed variation with a wide range of exposures between plants, countries, and between the different types of work task.

Exposure assessments are more reliable for industry based epidemiological studies than for population studies where subjects may be employed in a diverse range of workplaces. In terms of the ways in which exposures to agents have been categorised in epidemiological studies the 'ever/never' employed in a specific industry categorisation has been used in some population studies as a surrogate for exposure to specific agents, but this approach often has poor specificity. Generic job-exposure matrices (JEM's) are also usually found not to be valid or reliable, and their use has declined in epidemiological studies. Self-reported exposures from subjects usually perform better than JEM's, but they still have considerable variability in reliability and validity. Probably the best approach to assess exposure in population-based studies is through the use of expert evaluation. Clearly, this approach depends greatly on the knowledge and expertise of the assessor. Experts are better at assessing relative differences in exposure within a given context, e.g., a single workplace, than ranking differences across a range of diverse situations e.g., different processes or workplaces.

In conclusion, there is poor information about exposure and the prevalence of exposure for many of the carcinogens identified as relevant to the present work, and there has been little systematic collection of data for people exposed in GB since the 1990s. In using epidemiological evidence from countries other than GB or from one region of the country to another, consideration must be given to possible differences in exposure, which may be large.

Points for Consideration / Actions by HSE

- The CAREX database can be used to assess the number of people exposed but one must take into consideration the differences in exposure between countries (or regions), which may be large.
- There are examples where the CAREX data is unrepresentative of the situation in Great Britain, but in general, the ranking of agents using CAREX data seems broadly compatible with the expected estimates for GB.
- The top 20 agents listed in the CAREX database account for 97% of all workers exposed to carcinogens in Great Britain and adding the next ten agents increases this proportion to 99.5%, thus adding relatively little to the total.
- Further consideration should be given to 3 IARC Class 2B agents (therapeutic anti-neoplastic drugs, rubber constituents, and trichloroethylene), that are not found amongst the top 30 listed agents.
- There is poor information about exposure and the prevalence of exposure for many of these carcinogens and there has been little systematic collection of data prior to the 1990s.

2.3.2 Methods for Calculating Attributable Fraction for Occupational Cancer: Kyle Steenland summarised the different methods that can be used to determine the attributable fraction (AF), which is defined as “the fraction of cases of a disease which would be avoided in the absence of the risk factor”. The attributable fraction can often be calculated from the epidemiological literature. To calculate an AF you need to determine a relative risk (RR) for the factor and either the percentage of the population exposed, or the percentage of cases exposed. Case-control studies provide both an estimate of the RR, and of the percentage of the population (or cases) exposed. Alternatively, cohort studies of specific exposed groups can be used to estimate the RR, while an estimate of the percentage of the population exposed is derived from ancillary sources (e.g., population surveys). Often a meta-analysis of existing studies will provide the best estimates of RR, and similarly the relevant percentage of the population (or cases) exposed may be taken from several case-control studies.

Formulae can be used to determine the variance of these AF's but are unwieldy and may incorporate only random error whilst omitting other sources of uncertainty. Monte Carlo simulations may be preferable for estimating AF variance. Caution must be applied in extrapolating AFs from specific studies to a target population of interest (e.g., the GB population). In some instances, it may be that existing literature provides a range of attributable fractions, which can be adopted without re-

calculation of study-specific AF's. One might adopt a weighted average of these AFs and estimate the variance around these averages.

Other important issues include the latent period following exposure, how to estimate the percentage of ever-exposed versus those exposed at one point in time; and whether exposure is increasing or decreasing over time. Other considerations include which exposure/cancer associations are well established; whether to use incident cases or mortality data; whether to use DALYs (disability adjusted life years) in addition to AF's; whether separate AF's should be calculated by gender or social-class; and finally whether the level of exposure should be considered in addition to exposure or non-exposure.

Points for Consideration / Actions by HSE

- Caution must be applied in extrapolating AFs from specific studies to a target population of interest (e.g., the GB population).
- Important issues to recognise are the latency, how to estimate the percentage of ever-exposed versus those exposed at one point in time; whether exposure is increasing or decreasing over time.
- Other considerations include which exposure/cancer associations are well established; whether to use incident cases or mortality data; whether to use disability adjusted life years in addition to AFs; whether separate AFs should be calculated by gender or social-class; and whether the level of exposure should be considered in addition to exposure or non-exposure.

2.3.3 Estimating Reductions in Cancer Burden Following Reductions in Exposure: Ben Armstrong summarised how the nature of the exposure or dose-response relationship affects the nature of the attributable fraction and how analysis of this relationship can be used to inform decisions about interventions (and limit setting) to reduce the level of exposure in the population. The key decision is whether it is better to reduce exposure at high concentrations (usually a small population), or to reduce exposure at low concentrations (where the exposed population can often be large), or to reduce exposure across the board?

There are two baselines of potential interest for attributable fractions: (i) where exposure has been eliminated and (ii) where the exposure has only been reduced. The first is the usual baseline but the second may be the more practically relevant. The overall fraction due to exposure refers to the fraction of cases due to total exposure in a population (baseline (i)). This can be decomposed into parts due to exposure at different levels, and hence the fractions due to exposure in an original and in a reduced but non-zero distribution can be estimated. From this we can estimate the proportion of cases that can be prevented by a reduction rather than elimination of exposure (baseline (ii)).

Under circumstances where there are only two exposure categories 'exposed' versus 'non exposed', the distribution is binary and the attributable fraction exposed can be determined using standard formulae. It is also possible to calculate the attributable fraction at a baseline of 'no exposure', whether based upon a binary classification of exposure category, or using an index of continuous exposure. These fractions can be determined even for a binary classification using only data on the proportion of the population that is exposed, although this approximation is poor where other major risk factors correlate with exposure for the same population. For continuous exposure distributions it is possible to calculate the attributable fraction at baseline if exposures along specific points of a distribution curve are known.

By modelling the exposure distribution and the attributable fraction relationship it is possible to explore the influence of the exposure distribution on the distribution of the size of the population at risk. For linear dose-response relationships, the modelled distribution of the attributable fraction at baseline closely follows that of the shape of the exposure distribution. Using this model it is possible to explore the effect of shifts in the exposure distribution, for example a linear exposure model where

the distribution of exposure is shifted to a large number of people exposed to low levels. Similarly it is possible to determine the effect of introducing new exposure limits upon the attributable fraction for those exposed to doses below the exposure limit. Consequently the contribution of exposure to the attributable fraction depends upon the exposure distribution and the shape of the exposure-response relationship.

When applied to an intervention model it can be shown that it is the impact of the intervention on the mean exposure that drives the changes in the attributable fraction. However, to carry out this modelling it is necessary to assume that the relative risk is the same as the lifetime relative risk, and that other major risk factors are little correlated with exposure. This analysis does not address the issue of timing of exposure or latency of effect, or the influence of age of exposure and the rate of exposure. A linear exposure-response implies that the total burden of cancer depends only on the value of the mean exposure. However, for non-linear exposure-response relationships, determining the impact on the attributable fraction is more difficult. This method has been applied to data on exposure to polycyclic aromatic hydrocarbons from diesel exhaust emissions and has demonstrated that the largest numbers of excess cases are associated with the many more people exposed to low levels rather than the smaller population exposed to high doses.

This leads to the slightly provocative conclusion that the total burden of cancers due to exposure may be increasing due to a larger number of workers exposed to low doses, rather than due to small numbers of workers exposed to high concentrations. If this is the case, then occupational exposure limits (OELs) may not be the best way to reduce the burden of occupational cancers. Of course this depends on the assumption of a linear exposure model, but is there a better one? Other examples where the burden is largely 'low dose' exposure include non-ionising radiation and ambient air pollution, and this possibly may apply to asbestos in future.

There are two objectives that HSE wishes to address, the first is to minimise the number of persons exposed to a level of risk in excess of what is acceptable, and the second is to reduce the total burden of cancers. However, these two objectives may lead to different policies and the choice between these two options is value-based rather than science-based. In summary, the effect of reduced exposure can be determined on the basis of new and old exposure distributions. The exposure-response relationship is important and the 'residual' burden may depend strongly on the 'extrapolated' shape of this relationship and may consequently be proportionately large.

Points for Consideration / Actions by HSE

- The contribution of exposure to the attributable fraction depends upon the exposure distribution and the shape of the exposure-response relationship.
- When applied to an intervention model, for a linear dose-response relationship, it can be shown that it is the impact of the intervention on the mean exposure that drives the changes in the attributable fraction.
- For non-linear exposure-response relationships, determining the impact on the attributable fraction is less straightforward.
- The total burden of cancers due to an exposure may be increasing over time due to a larger number of workers exposed to low doses despite smaller numbers of workers exposed to high concentrations.
- Occupational exposure limits (OELs) may not be the best way to reduce the burden of occupational cancers, but this assumption depends upon whether the linear exposure model is the correct one.
- There are two objectives that HSE should address, the first is to minimise the number of persons exposed to a level of risk in excess of what is acceptable, and the second is to reduce the total burden of cancers. However, these two objectives may lead to different policies and the choice between these two options is value- not science-based.

2.3.4 Some Issues Relevant To The Occupational Burden Of Cancer: In leading this discussion, David Kriebel emphasised the need to recognise that most causes of cancer are environmental and therefore in principle preventable. However, most environmental causes are unknown and unfortunately many differences in cancer rates between countries/industries/occupations cannot be explained by known factors. It therefore seems likely that the known occupational carcinogens are only a fraction of the total occupational causes of cancer, but we do not know how large a fraction they are.

We need therefore to consider the relevance of ‘agent-’ versus ‘exposure-’ based approaches to determine the attributable risk. The agent- based approach identifies carcinogens used in occupations and determines the prevalence of use, exposure, and attributes the risk to the occupation. The exposure-based approach identifies those occupations with elevated risk, tries to remove the effects of non-occupational confounders and then determines the rest as due to occupational causes. The second exposure approach has been used to demonstrate that for lung cancer, for different occupations, the variation in cases observed is too large to be explained by smoking alone as a confounding factor. The problem generally is of widespread, low level exposure amongst larger numbers of individuals. Under these circumstances this may give rise to more cases of disease than small numbers exposed to higher exposure and risk. There are many examples where there is widespread 'low-level' exposure to carcinogens for example formaldehyde fumes (released from clothing in stores) and diesel exhaust exposure for truck drivers and taxi drivers.

It is also necessary to consider the effects of factors that interact with carcinogens, modifying (enhancing or reducing) the overall risk of cancer, for example asbestos & tobacco smoke and arsenic & tobacco smoke and the risk of lung cancer. When investigating low-level exposures there are methodological difficulties that have limited our understanding.

Exposure may also advance the onset of cancers that would have happened anyway and those should be considered ‘exposure-related’ and a part of an excess burden of disease. This excess fraction is not readily estimated from epidemiological data. The central question is whether occupational exposure advances the onset of pre-existing cancer and the problem is that we know very little about this. There are two different scenarios, through which this might occur. First, 'classical' carcinogens may act alone or in combination with other factors and in some exposed people they accelerate onset of a tumour that would have happened without the exposure. In the second scenario, chemical, physical or psychosocial exposures may act as promoters, accelerating the development of tumours that have been initiated by occupational or non-occupational causes. These promoters may not be genotoxic, and thus may escape the conventional approaches to identifying potential carcinogens.

The influence of confounding risk factors may be overestimated, but a more likely occurrence is that relative risks will be underestimated through non-differential exposure misclassification. Other sources of uncertainty include non-comparable relative risk estimates derived from different studies or different study populations. Distributions of exposure may also be different, and unaccounted for risk factors and effect modifiers may be involved. The patterns of exposure over time may also vary.

The acceptable level of this uncertainty may be different for a priority-setting process than for a 'listing' exercise such as that carried out by IARC. Consequently the best guess may (still) not be very good but we may be forced to use it! It is therefore important to tell policy makers how much we do not know and make the case for further research and for the importance of continued monitoring. A lower level of evidence may be needed to recommend controls on a hazard that has other negative effects (i.e., non-cancer or environmental impacts). This could be achieved by carrying out a comprehensive (descriptive) assessment of what has (or has not) been achieved with control of exposure. Then the major sources of uncertainty should be determined and the case for research made to fill any knowledge gaps.

A two-tiered approach to HSE’s burden calculation was recommended. First, a comprehensive, descriptive assessment of what has/has not been achieved in occupational cancer control should be presented, identifying major sources of uncertainty in estimates of occupational cancer burden. This

would make the case for continued research to fill knowledge gaps. Second, a set of “high priority” hazards should be identified, consisting of those for which the evidence base is very strong (IARC class 1, 2A), the cancer site is prevalent, and the exposure is quite common. Sensitivity analyses should be included to describe the range of plausible burden estimates. This two-tiered strategy would make it clear that the sum of all of the “high priority hazards” is not the totality of the problem of occupational cancer, but that it is the soundest place to look for guidance on short-term control policy. Finally, there should be an assessment to identify occupations with unexplained elevated risks and target these for further research. Using the agents-only approach leaves the impression that the full burden of occupational cancer is known and can be enumerated within the IARC list. This is not in the best interests of public health nor HSE.

Points for Consideration / Actions by HSE

- It seems likely that the known occupational carcinogens are only a fraction of the total occupational causes of cancer but we do not know how large a fraction they are.
- Exposure may advance the onset of cancers that would have happened anyway and these should be considered ‘exposure-related’ and a part of an excess burden of disease. This excess fraction is not readily estimated from epidemiological data.
- Policy makers need to be told how much we do not know, and the cases for further research and for the importance of continued monitoring should be made.
- A lower level of evidence may be needed to recommend controls on a hazard that has other negative effects (i.e., non-cancer or environmental impacts).
- Using the ‘agents-only’ approach leaves the impression that the full burden of occupational cancer is known and can be enumerated within the IARC list. This is not in the best interests of public health nor HSE.

3.0 Discussion Session

Identifying Priority Carcinogens, Cancers and Carcinogenic Processes

Following the introductory talks, the participants were asked to join one of four discussion groups to develop a prioritised list for GB of occupational carcinogens (and carcinogenic processes) for specific cancer sites. Each group was provided with information on carcinogens belonging to the IARC Group 1 and 2A, and occupations associated with exposure to these agents. On the second day of the meeting, the groups were asked to identify the most appropriate methods and data sets to assess the 'attributable' fraction for the carcinogenic agents and sites that they had prioritised. Each discussion group consisted of national and international experts in epidemiology, statistics, medicine, toxicology and hygiene. The following passages summarise the discussions and conclusions of these groups.

3.1 Respiratory Tract Cancers

Members of group: J Jaakkola (*Chair & Rapporteur*); J Osman; B Armstrong; M v Tongeren; P Vineis; A Saleem; P Howden.

3.1.1 Selection of priority respiratory carcinogens and carcinogenic processes: The frequency of occupational respiratory cancer is very high compared to cancers at other organ sites. We considered cancers of the lung, mesothelioma (almost entirely due to occupational exposure), larynx, lips, tongue, pharynx, and nasal passages. In considering, the carcinogenic risk factors we assumed that they overlapped closely for these sites. Our primary focus was lung cancer as the disease with the highest incidence and a high rate of fatality (life expectancy after diagnosis may be as little as a few months). We included those exposures where there was significant evidence such that the carcinogen could be classified as either an IARC 1 or 2A agent. We also drew heavily upon the studies by Siemiatycki *et al* (2004) and Kauppinen *et al* (2000) for 20 of the top agents and used the GB CAREX data set to estimate numbers of people exposed. Agents that were not relevant to exposure in GB (i.e., lack of exposure or small number of exposed individuals) were excluded from the analysis.

The priority listing of these agents was based upon evidence contained in the CAREX and NEDB datasets and evidence published by HSE as EH64 criterion documents. We considered those agents where the evidence of human carcinogenicity was strong and established their relevance according to whether the agent (or particular process) was used in GB in substantial amounts. Concern was expressed about the emphasis on IARC criteria because lung cancer related to particular occupations has been reported even where the candidate carcinogen was not identified. It is also likely that the size of the exposed population recorded in the CAREX database is an overestimate of the exposed GB population. Some published estimates of risk factors, and/or exposed populations may represent data aggregated from studies across many countries.

In addition to weighting these agents based on the total proportion of the working population in GB exposed to these agents, we also had to address other questions, for example, the size of the exposed population and the exposure distribution. It may be necessary to include situations in which many people are exposed to low levels, but to exclude situations where small numbers are exposed to potentially high levels. For some occupations (and cancers) exposure to more than one carcinogen may occur e.g., as with combustion products. From a scientific perspective, we may be interested in a specific carcinogen, but for the purpose of intervention what really matters is control of exposure to complex mixtures, e.g., environmental tobacco smoke.

Other issues discussed included how to determine 'effect estimates' for these agents, and how to determine levels of exposure amongst the general population? An agents-based approach is more useful to obtain generalised effect estimates, but when you consider agents according to the type of industry, the effect estimates are driven more by national variations and characteristics of the working population. The exposure effect data can be collected using large case-control studies such as the Liverpool Lung Project being carried at the Roy Castle International Centre for Lung Cancer Research in Liverpool in which data on the probable point of first exposure to tobacco smoke (and other

substances) is being collected from a cohort of ~10,000 people. This data set will be reviewed by a panel of experts over time as disease develops.

A growing problem in some sectors of GB industry is the changing population of exposed people, with increasing use of contract workers. The estimated number of contract workers in the GB may be inaccurate but these people do jobs where often the highest exposures are encountered. With regard to delivering public sector targets, HSE may need to set its priorities on those agents where the use of a carcinogen (or carcinogenic process) is increasing, or alternatively where the exposed population is increasing. Another priority issue is the availability of information on preventative measures. For established patterns of exposure, HSE could expect proper controls to be in place amongst larger businesses. Can they police practice amongst many small companies? The information about use and exposure with regard to sector or business size is only available in HSE/ HSL surveys for a few of these agents or processes, e.g., polycyclic aromatic hydrocarbons (PAH) exposure.

It may also be important to understand the distribution of exposure i.e., whether it is linear, has a threshold, is non-linear, or dichotomous. The use of 'mean' exposure values can give the wrong picture as this does not account for different chemical species e.g., hexavalent chromium, where the potential risk of exposure may be higher. We need to be cautious when interpreting exposure databases particularly those collected by HSE since the data may not represent a true random sample being more representative of exposure post enforcement activity. Data have been collected systematically for some industries but not for others, e.g., silica exposure is well represented in the NEDB database but many other agents are not.

The final product of this exercise may be interventions with the most impact on the highest numbers of exposed, or those at highest risk. It may be best to address some groups with a generic intervention, but others need intervention tailored to a specific substance or process. For respiratory cancer, the largest exposed population and high exposure situations may need to be the focus of this exercise whilst ignoring smaller subsets where exposures are well controlled. Should we consider ignoring agents (processes) where the reported deaths are fewer than two per year?

This argument could be applied to beryllium because nationally there is a small group of people who work in a specialised industry where currently high standards of control on exposure exist alongside regular health surveillance of the workforce. However, there are risks in this assumption if the historical records of exposure are incomplete, or where there are underlying changes in the size of the industry. Furthermore, HSE has introduced limits that have succeeded in reducing exposure, and this change may affect the future trends compared to past figures for respiratory cancers. HSE needs to recognise that if you have a 10-year target with an outcome that could take 30 years, it will not be able to demonstrate the impact of an intervention in terms of reduced incidence of disease. This suggests that HSE needs targets for exposure where the disease outcome is long-term, and targets based upon disease outcome only where the disease free interval is short.

Sources of exposure that also need further consideration include the relationship between laryngeal cancer and acid mists, arsenic, formaldehyde and chromate exposure. Other agents that should be removed from the priority list include aluminium and external ionising radiation, because of the low expected number of cases per year, the low estimated numbers exposed, and the low relative risks. The number of people exposed to arsenic via the respiratory route is considered very small, and in recent times, controls on exposure have considerably improved in GB with a consequence that only 1-2 cases are now reported per year. The number of people exposed to arsenic via the skin is much higher if one includes refining, electronics, chemicals, semiconductor production and handling of wood preservatives. An estimated number exposed via this route is ~25,000.

If the relative risk across the exposed population is low then it is likely that the number of attributable cancers will be small, but if the exposure is concentrated in a sub-group with a higher relative risk then a larger number of cancer cases may be observed. Following the introduction of European exposure limit, and withdrawal of arsenic from wood preservatives (as well as the use of improved controls in some industries), we propose that arsenic not be included as a priority agent in this list. Formaldehyde

may need to be considered in terms of its risk of nasopharyngeal cancer, although this is a rare cancer. For chromium VI there are ~130,000 exposed workers and we agree that this should have been included in our priority list. With regard to diesel exhaust this should be subsumed under the PAH category and it is clear from the data presented by Ben Armstrong that PAH mixtures continue to be a problem.

The major occupations and agents for respiratory and oral tract cancers in GB are listed in Table 3.1. Further work on this 'prioritised agent' list will need consideration of 'effect estimates' based upon the GB data as well as information about the dose response relationship between exposure and risk. Population based case control studies as originally proposed by Doll and Peto (1981) should be considered either for all cancers or focusing on lung cancer alone. Data from other categories of jobs and working conditions specific to GB must also be considered. We need to estimate the number of cancers occurring each year, changes in exposure, the intensity of exposure and related variables. It is important that the quality of the exposure data is good. Historically the focus of activity has often been on small occupational groups with unusually high exposures, yet from the perspective of estimating the global burden these populations may not be relevant. Whilst there may be a political price for ignoring a sub group where the disease incidence is high, the danger is that the total burden is largely occurring elsewhere amongst many exposed to smaller concentrations of the carcinogen.

IARC Group 1	Exposed workers (x 10 ³)	IARC Group 2A	Exposed workers (x 10 ⁴)
Asbestos	95	PAH	106
Cadmium	36	Hair dressing chemicals	191
Involuntary smoking	1300	Inorganic acid mists	42
Iron and steel	100	Rubber industry	12
Nickel salts	42		
Painters	150		
Crystalline silica	590		
Radon	560		

The issue of whether IARC Group 2B agents should be included on the priority list was discussed. Apart from the lack of strong evidence of their human carcinogenicity, there are large numbers of people occupationally exposed to these agents. For example, types of polycyclic aromatic hydrocarbons e.g., benzo(a)pyrene, and benz(a)anthracene, and alpha-chlorinated toluene. Some of these chemicals are well controlled in manufacturing but many downstream users use inadequate controls. Mineral oils are used in welding, steel cutting and cooling agents. Surveys have shown the general levels of exposure to these oils are low but there are groups e.g., glass manufacturers where levels of exposure are quite high. It is estimated that ~12,000 people are exposed to rubber and recycled rubber products and the risk of bladder cancer and lung cancer needs to be considered.

The calculation of the future burden of occupational respiratory cancer based upon current exposures was considered. This would require collection of good data for current first exposure to enable future trends to be predicted. This work could help to set future standards for controls but would have to take account of continuously changing exposure profiles and dose-response relationships.

Points for Consideration / Actions by HSE:

- The frequency of occupational respiratory cancer is very high compared to cancers at other organ sites.
- Concern was expressed about the sole emphasis on IARC criteria.. Lung cancers related to occupation have been reported even where the candidate carcinogen was not identified. It is also likely that the size of the exposed population recorded in the CAREX database is an overestimate for the exposed GB population.
- A growing problem is the changing population of exposed people with increasing use of contract workers who do jobs where often the highest exposures are encountered.
- For the purpose of intervention control on exposure to complex mixtures, e.g., like environmental tobacco smoke, should be considered carefully.
- HSE may need to set its priorities where the use of a carcinogen (or carcinogenic process) is increasing or where the size of the exposed population is increasing.
- We need to be cautious when interpreting exposure databases particularly those collected as part of enforcement activity.
- The final product of this exercise may be interventions which impact on the highest numbers of exposed or those at highest risk. This may be met by generic interventions but in some cases will require intervention tailored to a specific substance or process.
- Historically the focus of activity has often been small occupational groups with unusually high exposures but the global burden of these populations may not be so great. There may be a political price for ignoring 'subgroups' where disease incidences are high, but the danger is that the total burden is largely occurring elsewhere amongst many more exposed to smaller concentrations of carcinogens.
- The calculation of the future burden of occupational respiratory cancer based upon current exposures was considered. This would require collection of good data for current first exposure to enable future trends to be predicted. This work could help to set future standards for controls but would have to take account of continuously changing exposure profiles and of dose-response relationships.

3.1.2 Selection of methods and data to determine attributable fraction for respiratory carcinogens and carcinogenic processes

Table 3.1.2. The priority list of respiratory cancers, carcinogens and carcinogenic processes

Cancer	Carcinogen
Mesothelioma	Asbestos
Lung cancer	Asbestos
Lung cancer	Diesel exhaust
Lung cancer	Chromium
Lung cancer	Radon
Lung cancer	Cadmium
Lung cancer	Arsenic
Lung cancer	Nickel
Lung cancer	Iron and steel founding
Lung cancer	Silica
Sinonasal cancer	Wood dust
Sinonasal cancer	Leather dust

For the list of priority agents, the attributable risk estimates for each carcinogen and the relationship between each agent and cancer type was discussed.

Mesothelioma – Asbestos: The aetiological fraction is very high for asbestos and mesothelioma and any intervention in relation to asbestos will also impact on the number of asbestos-related lung cancers. One recommendation, if possible, is that the data be disaggregated to show the relationship with exposure in different occupations and their contribution to the total attributable number, but this method can only work with a retrospective analysis.

To calculate the future trends, information about current exposures related to these cancers will be required. HSE holds information on the numbers of people registered for particular types occupations e.g. asbestos removal, but not for example electricians and plumbers. There are reasonable effect estimates that can then be applied to the current exposure information. In addition, we need information about the mean number of people exposed and the distribution of exposure. However, it is unlikely that there are sufficient data to construct exposure distributions for each subgroup and so expert judgement will be required to estimate these exposure distributions.

Lung Cancer–Asbestos: Two different approaches could be used to determine the current burden due to past exposure. The method outlined by John Hodgson and Andy Darnton, or via the more formal meta-analytical approach that has previously been used for polycyclic aromatic hydrocarbons. This will need data on past exposure distributions and estimates of the dose-response effects will have to be taken from the published literature. For this purpose the incidence of mesothelioma could be used in replacement for mortality data (although mesothelioma is invariably and rapidly fatal) and because there is a clear relationship between the incidence of mesothelioma and lung cancer, future estimated incidences could be derived.

However, to estimate the future burden, more accurate information about current exposures need to be estimated, along with dose-response data for lung cancer. There are published papers that contain effect estimates for the GB population, although these are mostly specific cohort studies, and if necessary data may need to be drawn from the world literature. A key issue is the influence of the type of asbestos fibre and it may be necessary to determine different dose-response estimates for each fibre type as well as the fraction of the population exposed to these different fibres. This needs to take account of the latency period that is different for lung cancer compared to mesothelioma.

With regard to future estimate of burden, it needs to be recognised that asbestos is being continuously removed and levels of exposure in future will continue to reduce. However, if a ‘clear cut’ view, emerged that e.g., amosite is the worst fibre type, HSE may have to reconsider how it regulates and enforces compliance within particular limits. At present, all licensed users are registered and given equal importance in terms of their job description but this may need to change if a more focused strategy is to be developed.

Lung Cancer - Silica dust: HSE survey data have shown that this affects several sectors of industry such as quarry workers; granite polishing; construction workers; tunnelling workers; concrete casting and sandblasting activity. The only category of worker where there does not seem to be an increased risk of lung cancer related directly to silicosis is coal mining, possibly because coal disintegrates into preformed small particles whereas cutting of other rocks generates fresh reactive particles. In some of these sectors, the use of new technology has reduced exposure.

The evidence that has been collected from experimental studies suggests that the level of risk is related to cumulative exposure. The question of whether the occurrence of silicosis can be used as a marker of risk for cancer was discussed. In particular, was there a relationship between excess numbers of lung cancer and silicosis cases? This may depend upon whether the exposure-response relationship is different for the two diseases.. A meta-analysis of these risk categories for lung cancer in relation to the cumulative exposure has been carried out but can, these data be translated into risks within the GB?

The exposure-response data for silicosis are well defined but the risk for a given dose is much higher than for lung cancer. This, together with the shape of the relationships raised some doubts as to whether you could draw a relationship between the two. Extrapolation might only be possible if the two dose-response relationships were parallel. A previous attempt by HSE to determine the attributable fraction of cases made use of relative risk estimates from the United States and these were applied to a hygienist's estimate of the numbers exposed (at different levels) to silica. However, the number of silicosis cases estimated by this method, was hugely in excess either of the number diagnosed or compensated, and the number of registered deaths for the disease. This discrepancy may have been a result of silicosis deaths being registered under other causes of death e.g., pneumoconiosis, or because the estimated exposure levels were too high. The assumption was of a linear dose-response relationship with most cases arising from the low exposed category.

In contrast, the Institute of Occupational Medicine (IOM) study on Scottish coal-miners (Buchanan D, Miller and Soutar, 2001) demonstrated a curvilinear (quadratic-like relationship) between silica exposure and silicosis risk (as assessed by radiological tests). Using those data, the ratio of silicosis cases to lung cancer cases was 2:1. A meta-analysis of other data, which summed the excess silicosis and lung cancers across all the studies, resulted in a similar estimated ratio despite major differences between the studies. It was concluded that the number of excess lung cancers was related to the number of silicosis deaths and that the number of silicosis deaths is not far removed (probably up to 2 fold higher) than the number of registered cases. It has to be recognised that silicosis deaths are rare compared with lung cancer deaths.

Lung Cancer - Diesel Exhaust: The approach adopted for this agent was based upon that used for asbestos (but not with the mesothelioma link) using past exposure data and dose-response estimates. In this case, there are problems in calculating current burden based upon past exposures. There is a large overlap between occupational exposure and exposure in the general population particularly in large polluted cities. The second problem is how to choose the best estimate of the exposure-response relationship since this is very difficult to establish. There are many published studies on occupational exposure to diesel exhaust but few give information about dose-response relationships.

HSE has commissioned several studies on this subject (e.g., a GB survey was carried out 1994/5 to look at exposures for jobs such as train driving, forklift truck drivers etc). However, this means that it may only be possible to construct a job exposure matrix for diesel exposure during the mid 1990s. During this period it is likely that exposure amongst the public has increased whereas awareness and use of controls have improved in many workplaces. In the absence of good dose-response data it may be necessary to use an 'ever / never' category of exposure with regard to past exposure. It may be possible to aggregate data from published studies but it is common for studies to report quite different levels of exposure making it difficult to compare results.

With regard to the future burden, we do not have recent exposure data so we may need to assume proportionate exposures. For example, we could assume that exposure levels have approximately halved between 1970 and 2000, although for some occupations they may have remained the same. If this reassessment of the data is to be completed quickly for the current exercise, then decisions will have to be made promptly. If HSE wants to develop performance indicators and track the future burden of cancers, this cannot be just a 'one off' exercise. In addition to polycyclic aromatic hydrocarbons there are many other fine particles in diesel exhaust, as well as dusts, and whilst there are measurements of the PM 2.5 fraction as well as total respirable dust, we may need more appropriate exposure indicators.

Lung Cancer - Radon: More quantitative assessments are required to determine exposure to this agent, and whilst we know the causal agent and how to measure it, we have measurement data only for small numbers exposed in a few occupations. However, data on non-occupational exposure (residential) are available on a regional basis. One problem is that exposure to radon in

work is probably less than in the home environment (for the same region) and to a certain extent more of an avoidable risk. In GB there are no underground mines in the areas of highest exposure except for some tin mines, which have closed for commercial production.

Exposure to radon can vary hugely from house to house in the same region, and depends upon the structure of the house, and it is unlikely that exposure data are widely available for individual workplaces. It might be more cost effective to reduce exposure in work plants rather to attempt a reduction of exposure within affected homes, and subsequently reduce exposure for many people at limited expense. HSE should consider re assessing the numbers of deaths related to radon exposure and data may be available from the HPA who have mapped environmental levels in different parts of GB.

Lung Cancer - Iron And Steel Foundries: There are measurements of the exposure to respirable dust particles in these industries, and there may be 'effect estimates' in the literature. The carcinogenic agents that may be encountered are varied and include silica dust, soots, gasses, and polycyclic aromatic hydrocarbons. Respirable dust measurements provide a reasonable proxy for the exposure levels to these other agents. PAH measurement could also be used as a surrogate, but the groups at risk will need to be identified as well as the risks associated with particular occupations. Occupational mortality data or a combination of this and other measures could also be used to determine the attributable fraction. There are measurements of past exposures as well as current exposures. Levels of exposure may be high but under circumstances where it is not possible to identify all of the potential carcinogens. This suggests that a systematic review of the literature on jobs and industries should be considered. It will not be possible to disaggregate such a complex matrix within the time that is available for this exercise.

Estimating the future burden will be challenging because there have been major changes in the workforce in this industry, and the introduction of new technologies. It is possible that changes in total exposure could be used as a predictor of future burden. Data collected by HSE/HSL show evidence of large variation in exposure between foundries, and within foundries for different work tasks. Exposure standards have been set for total dust and compliance with this limit is regularly monitored. A meta-analysis of the exposure-response relationships that have been published may help to provide estimates of exposure, and the populations exposed. The attributable fraction may be directly calculated from these data based upon classification of industry type and using cohort studies e.g., foundry workers.

Sinonasal Cancer - Wood dust: The relevant occupations in woodworking and wood processing are well recognised, and the appropriate data on exposures could be obtained from the NEDB. However, it needs to be recognised that people in these occupations move jobs frequently, and consequently it is easy to underestimate the numbers exposed. Other published studies and databases are available on levels of exposure and the numbers exposed in GB industry and in other European countries. The key issue is the level and distribution of exposures and risks are generally considered higher for hardwood than softwood dust. The majority of woodworkers are exposed to softwood dust but the use of exotic hardwoods is increasing.

There are GB based cohort studies in woodworking factories that can provide disease incidence, or mortality rates, occurring over several years in these factories. However, the incidence data may underestimate the numbers affected compared to the use of routine mortality statistics. The literature also contains studies from other countries in which the relation between nasal cancer and wood dust has been examined and not just in furniture manufacture. These general risk estimates may be applicable to GB woodworkers. Data on nasal adenocarcinomas from GB cancer registrations may also help to identify many of the occupational cases because the disease is largely driven by exposure in work. There are five occupational categories of woodworker in the registration data, and these all have potential for exposure to wood dust.

Nasal Cancer - Leather Dust: The risk of nasal cancer is largely related to exposure from work in the boot and shoe industry. The number of workers exposed is small, and it may be necessary to determine the number of cases using data in the decennial supplement or cohort studies of this industry. This would help to estimate the proportion of all exposed workers in the national cohort. It is recommended that a limited effort be put into this category of exposure.

Points for Consideration / Actions by HSE:

- **Asbestos:** With regard to future estimates of burden it needs to be recognised that asbestos is being continuously removed and levels of exposure in future will continue to reduce. However, if a 'clear cut' view emerged that e.g., amosite is the worst fibre type, then HSE might have to reconsider how it regulates and enforces compliance within particular limits. At present, all users are registered and given equal importance in terms of their job description, but this may need to change if a more focused strategy is to be developed.
- **Diesel exhaust:** A reassessment of the data is recommended, but needs to be completed quickly for the current exercise.
- **Radon:** HSE should consider re assessing the numbers of deaths related to radon exposure
- **Iron and Steel:** For the iron and steel industry a meta-analysis of the exposure-response relationships that have been published may help to obtain exposure-specific risk estimates for this industry.
- **Performance indicators:** If HSE wants to develop performance indicators and track the future burden of cancers this cannot be just a 'one off' exercise.

3.2 Hormonal & Genitourinary Tract Cancers

Members of group: T Fletcher (*Chair & Rapporteur*); P Boffetta; R Elliott; L Rushton; S Semple; M Goldberg; A Darnton; A Smith; D Morgan

3.2.1 Selection of Priority Hormonal & Genitourinary Tract Carcinogens and Carcinogenic Processes:

The cancers that were considered as part of this review exercise were ranked as either of definite interest; of possible interest, or definitely of no interest. In the data provided by HSE, there is established evidence of an occupational involvement for only two of the agents / cancer sites listed. The major site amongst this group of organs for which the evidence of occupational exposure is strong is for bladder cancer. We need to decide whether any of the other listed carcinogens are of sufficient concern to justify including them, and if not, the focus should be on bladder cancer. We also need to recognise that for common cancers such as breast cancer the evidence for involvement of chemicals is not clear.

Each agent on the HSE list was considered in relation to its IARC classification and important carcinogens that were missing were identified. For the chemicals for which the evidence of human carcinogenicity was weak with classification largely based on animal data, it was necessary to consider the likely effect on human organs and whether animal models were representative of human cancer. Another factor considered was how to interpret the evidence for risk associated with chemicals in the occupational setting, in circumstances where there was already a strong association with a non-occupational cause. For example, in France large studies of breast cancer amongst workers in the commercial sector have been started because this is a very common cancer.

Breast Cancer - Shift Work: The link between breast cancer and occupation is currently an area for much research although it was not clear whether a systematic review of occupational female breast cancer had yet been carried out. Marcel Goldberg informed the group that research

is currently being carried out in France, with a specific focus on work in agriculture and in the cosmetic industry. Breast cancer was more prevalent amongst higher social classes but this finding may have been skewed because this group are more likely to use breast cancer screening services. There may be no one strong occupational risk factor and links to chemical carcinogens are even less clear. Current research has investigated the link between stress and cancer amongst air hostesses who do shift work, particularly those involved in long haul flights. Nurses, and maritime radio operators are other groups who have been studied in this context. One limiting factor is the underreporting of occupational illness amongst women who work in traditionally male orientated businesses.

Cervical Cancer: Environmental dioxins (e.g., 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)) are risk factors for cervical cancer and exposure to these agents is generally considered to be increasing but the evidence for an occupational link is weak. Dioxins are the subject of an existing substances review within Europe and there is a division of opinion about the human carcinogenic status of these compounds. The conclusion must be that at present the evidence for an occupational link to cervical cancer is weak. The link to environmental tobacco smoke should be considered because a large population of workers is exposed and because it should be more practical to control chemical exposure in the workplace than amongst the general population. Another candidate carcinogen is perchlorethylene for which there is anecdotal evidence of indirect exposure via partners who work in e.g., engineering.

Uterine Cancer: The risk profile for uterine cancer was considered to be very similar to breast cancer but there is an absence of good data from human exposure to say whether this assertion is fully justified.

Ovarian Cancer: The populations most at risk are hairdressers and those who work in the motor vehicle industry. The original studies established a positive dose-response relationship between exposure to diesel engine exhaust and ovarian cancer. A Finnish study (Guo J, et al, 2004) has reported that the increased relative risk was driven by a cohort of workers exposed to grease on car components. These studies may need careful consideration about the use of gender specific risk estimates. Amongst those exposed to diesel exhaust, increasing numbers of women are being employed as drivers, but the current risk estimates are based on studies of men, so can these risk estimates be applied to women? Gender specific differences in risks for e.g., lung cancer, have been proposed but the evidence for them is weak.

Male Genital Cancer: There is no evidence of a major occupational risk, but links have been suggested for professional drivers exposed to heat or mineral oils and development of scrotal cancer. Exposure to mineral oil is more of an historical issue but there may be lifetime risk for those previously exposed. Further consideration of this form of cancer will require more evidence about relevant exposures, numbers of people exposed, and the relative risk in relation to occupation. There may not be sufficient evidence of a causal relationship.

Prostate Cancer: Long distance lorry drivers are considered at risk but there may be other relevant industries. In general, the supporting evidence is weak. A number of studies have suggested an association of testicular cancer and particular occupations, but this evidence is also weak. Evidence for a link to farming as an occupation is growing and an up-to-date systematic review may help to resolve this.

Kidney: Most studies have examined exposure to solvents and more attention should be paid to subtypes of polycyclic aromatic hydrocarbons.

Bladder: The association of occupation with bladder cancer is very strong and animal models suggest a potent link to specific chemicals. Many new chemicals are being introduced that potentially could also act as bladder carcinogens. The sectors of concern include the use of dye substances in the printing and textile industries, but there are preventative opportunities to deal with this exposure. However, existing estimates of the attributable risk for bladder cancer are

likely to depend upon past historic exposures. More recent changes in exposure, and in the size of the exposed population may need to be considered. Doll and Peto suggested that the level of bladder cancer should go down because of the elimination of particular chemicals but are we safe in making these assumptions in the light of new chemicals usage? The link to environmental tobacco smoke should be considered because a large population of workers is exposed and because it should be more practical to control exposure in the workplace than in other environments. A systematic review of the current literature could be considered to provide better estimates of risk, exposure and the exposed population. There is a latency problem for bladder cancer, so it will be necessary to infer trends from past exposures studies.

Thyroid: Ionising radiation is the only agent listed, and this is a well-established occupational risk factor

Conclusions: The priority organs are bladder, kidney and thyroid, and the evidence for occupational exposure causing prostate, testicular and breast cancers is weaker. However, the issue of female cancer and occupational risk needs to be treated carefully as this is a socio-politically important subject and cannot be ignored.

There are big gaps in our knowledge and this may need consideration for funding of research. Finally, the evidence of occupational causes for cervical, uterine and ovarian cancer is weakest of all.

It may be necessary, however, to consider the influence of confounding factors such as tobacco smoke since the numbers exposed at work are very large and this may increase the risk for development of major cancers such as breast cancer. An important issue is how to prioritise these carcinogens, in terms of the numbers affected, the severity of the risk, or the strength of evidence for the link. In this review, the priority has to be based on an association with increased risk and not based on how easy the problem is to prevent. It may be necessary to further classify associations in terms of 'well established', 'intermediate', or 'speculative'. This will require some judgement of the human hazards in addition to their IARC classification.

The most common occupations at increased risk appear to be in the manufacture of plastics and leather products, painters, and petroleum refinery workers. Most of these occupations have exposures to solvents and smoke. For those occupations that show an increased risk for several cancer types, the priority status of these carcinogens should be reviewed e.g., painters are potentially exposed to many reactive substances.

Points for Consideration / Actions by HSE:

- **The priority organs** are the bladder, kidney and thyroid
- **Breast cancer:** For common cancers, like breast cancer, the evidence for involvement of chemicals is not clear.
- **Breast cancer:** A systematic review of female breast cancer and occupation should be considered if one has not already been commissioned.
- **Female cancer:** There is under-reporting of occupational illness amongst women who work in traditionally male orientated businesses and the issue of female cancer needs to be treated carefully as this is a socio-politically important subject.
- **Bladder cancer:** A systematic review could be considered of the current literature on occupational bladder cancer to provide better estimates of risk, exposure and the exposed population.
- **Non-occupational causes of cancer:** Interpreting the evidence for risk associated with chemicals in the occupational setting in circumstances where there is already a strong association with non-occupational causes will be difficult.

3.2.2 Selection of methods and data to determine attributable fraction for hormonal and genitourinary cancers and carcinogenic processes.

Table 3.2. The priority list of hormonal and genitourinary carcinogens and carcinogenic processes

Cancer	Carcinogen
Urothelial cancer	Aromatic amines
Urothelial cancer	Aluminium manufacture
Lung/Urothelial cancer	Environmental tobacco smoke
Lung/bladder	PAHs
Thyroid	Ionising radiation

Aromatic Amines: The epidemiological evidence to disentangle the possible effects of PAHs and aromatic amines in the aluminium manufacturing industry is insufficient. Furthermore, aromatic amine exposures are difficult to translate from the past to the present using epidemiological data. The aromatic amines clearly associated with bladder cancer in the past are not used today and are not therefore relevant to the estimation of future burden. Bladder cancer was the second major occupational cancer listed by Doll and Peto but it does not appear to be as important today. However, some of the compounds for which animal carcinogenicity has been demonstrated are still being used today in the dye, printing, textile and rubber products industries.

The Health and Safety Laboratory have conducted a biological monitoring study of 4,4'-Methylenebis-2-chloroaniline (Evidence for an N-Glucuronide metabolite in the urine of workers exposed to 4,4' methylene bis- (2-chloroaniline) (MBOCA): HSL Report IR/L/OT/86/3) and there may be biological monitoring data for 4-methylenedioxyamphetamine (MDA). For MDA, there are only a small number of workers handling this, but it is added to many products. For other amines there are potentially very large numbers of workers exposed to low levels, and a smaller number exposed to high concentrations. To determine the current burden an estimate of the population employed in these 'high risk' areas is needed. It may be necessary to use relative risk estimates from studies of the rubber industry when considering risk of exposure to amines in other sectors. Whilst these risk estimates for rubber are likely to be over estimates, they are the best potential surrogate relative risk estimates for aromatic amine exposure.

It may also be necessary to request data from manufacturers and trade associations and to extrapolate from animal data, but caution will be needed because the metabolism of these chemicals differs considerably across species. The use of relative risk data from the rubber industry needs careful consideration. It represents a good example of a mixed exposure situation, but there are high levels of uncertainty in using these data. It may be necessary to model a range of exposure values and relative risk values to derive best estimates and this will require an estimate of variability in the existing data sets.

A 'population based' study has been completed in GB, and concluded that the majority of excess cancers were related to past exposures in the rubber and dye industries, but the plastics industry represented an emerging area of concern. Use of the published data implies that the total burden will have to be estimated by extrapolation. Published case-control studies are likely to give information about all carcinogens, not just aromatic amines, and many are based upon job industry categories and not exposures. More information is needed about the transformation of these chemicals in different human tissues, particularly for the aromatic amines, and for comparison with the metabolism of other types of potent hydrocarbon. There are Department of Health atmospheric pollutant studies that could help to answer this.

Aluminium Manufacture: The risk in this industry is principally associated with exposure to PAHs and bladder and lung cancers. There may be no value in considering aluminium

manufacture separately from the more general issue of PAH exposure unless there are other important carcinogens. This is compounded by the small size of the industry in GB and the use of automated production. This is something that HSE will need to decide in terms of resource allocation. Current burdens could only be estimated using data from aluminium production but the future burden may be better estimated in terms of polycyclic aromatic hydrocarbon exposure in general.

Polycyclic Aromatic Hydrocarbons: In France it has been estimated that there are more than 10,000 cases of bladder cancer per year whereas in GB the number is estimated to be ~13,000 cases per year. The major industries in the past were aluminium smelting and coke production, but these compounds are also found in environmental tobacco smoke and other general types of combustion smoke. There is no single measure of exposure because the range of exposure has been recorded to vary between 10 and 1000ng /m³. The Health and Safety Laboratory have published a report on exposure to polycyclic aromatic hydrocarbons (Dabill DW, 2003) and reviews are available from HSE. The NEDB also contains measurements for several different occupations. These data could be used to estimate current risk and may be of some value for estimating future burden for 'high risk' industries.

Environmental Tobacco Smoke: It is estimated that there are 1000 to 2000 lung cancers cases per year because of environmental exposure to tobacco smoke in GB. This data could be used to determine an attributable number but will not allow calculation of trends over time. It has been stated that the ban on public smoking could save 70 to 100 lung cancers deaths in Scotland each year. Is this an over estimate for the likely numbers if England also banned smoking in public? There are several meta-analyses of environmental tobacco smoke and meta analysis for exposure to tobacco smoke in different working environments that could be utilised. The analysis should not be restricted to the never smoker category since there can be an excess risk in those who also smoke at home. Occupational smoking could add to the risk from personal smoking and the additional risk for 'former' smokers is not increased compared to 'non smokers' when they work in the presence of cigarette smoke. HSE is interested in the burden of cancers attributed to environmental tobacco smoke but does not plan intervention work in this area because this is likely to be carried out by other government departments.

Thyroid Cancer & Ionising Radiation: Thyroid cancer risk is mainly caused by isotope exposure. We have good data on ionising radiation exposure in the workplace and those workers involved in plant decontamination usually have a high external dose over a short time period. Those exposed include the nuclear industry and medical radio imaging. For example, radiographers have an increased risk but this accounts for only a small number of cancer cases per year. Exposures may have changed, but many radiation workers have been studied in the past and evaluated for the nature of the dose-response relationship and the available data are of good quality. The GB Cancer Registry (<http://www.cancer-uk.org/>) may also demonstrate how many deaths are affected by occupational exposure.

Points for Consideration / Actions by HSE:

- **Exposure to amines:** To determine the current burden an estimate of the population employed in 'high risk' areas is needed.
- **Exposure to amines:** More information is needed about the metabolism of these chemicals in different human tissues, particularly for the aromatic amines and for comparison with the metabolism of other types of potent hydrocarbon.
- **Exposure to PAH in the Aluminium Processing:** HSE will need to decide on prioritisation for resource allocation. The future burden may be better estimated on the basis of polycyclic aromatic hydrocarbon exposure in general.

3.3 Digestive Tract, Skin and Brain Cancers

Members of group: C Soutar (*Chair & Rapporteur*); D Coggon; K Steenland; J Peto; M Nieuwenhuijsen; J Hodgson; L Levy; A Phillips; T Grimsrud

3.1.1 Selection of Priority Digestive Tract, Skin and Brain Cancers and Carcinogenic Processes:

In drawing up the list of target carcinogens for these organs the IARC Class 1 and 2A agents were included (specifically the top 30 agents identified by J Cherrie). The estimated number of exposed people in the GB workforce was also considered alongside additional evidence on the health risks associated with exposure. Low risk carcinogens were excluded, as were those for which the exposed population was small. To complete this review will require more information about the agents and the exposed populations, access to published estimates of risk amongst exposed groups; and comparable data from elsewhere, preferably Europe, if there are no suitable GB data. This will require translation of risks to the relevant GB populations. Age-adjusted mortality rates for these occupational cancers will have to be determined for GB, as well as incidence rates, which may need to be inferred from mortality data. Skin was considered the major target organ for occupational cancers in this group. Each of the target organs was considered with respect to each of the major carcinogenic risk factors. It was proposed that occupations e.g., painters or work in the rubber industry, rather than purely carcinogenic agents, should be the basis for assessing the numbers exposed and the attributable risk.

Liver Cancer: The first agent that was discussed was ionising radiation, for which there was not much evidence, that it played a role since liver cancers are rarely encountered in relevant occupations. There may however, be an increased risk following ingestion of radioactive material that accumulates in the liver. Radon is a cause of lung cancer but is not associated with liver cancer.

Viral hepatitis, which may occur in health sector workers from injury by contaminated needles, is a cause of liver cancer. However, at the population level there is a significant decline in occupationally acquired hepatitis because of large-scale immunisation programs and better safety procedures. As the numbers of cases are small and appropriate intervention programs are in place, this agent should not be considered a priority. However, HSE should consider monitoring this area.

Lung (as well as skin and gastrointestinal tract) cancers are associated with increased arsenic content in drinking water and with exposure to arsenic by inhalation during copper smelting. However, the attributable fraction for liver cancer from these exposures is likely to be low compared to lung cancer, probably reflecting the route of exposure. Copper chrome - arsenic mixtures are not used so much and are being phased out of use. With this low prevalence of exposure, arsenic must be considered of lower priority for this exercise.

For vinyl chloride, the relevant industrial databases suggest that high exposures are being eliminated, but it is not clear whether 'low level' exposure remains a problem. Furthermore, waste disposal sites are associated with increased exposure, but fewer than two attributed cancer cases per year have been reported for this exposure situation. Alcohol consumption is a possible confounding factor that needs to be considered.

Combustion of PVCs can also contribute to exposure and there may be some value in monitoring levels close to incinerators sites and waste tipping sites although these are not exclusively occupational exposures. Background rates of angiosarcoma of the liver are so low that if there is an increased risk associated with work around waste disposal facilities then it will show up. The Institute of Environment at Leicester (IEH) published a report in 1977, which found no increase in liver cancer amongst those living around incinerators (Health Effects of Waste Combustion Products: Report 7: 1997. MRC IEH, Leicester). However, vinyl chloride

has been added to the top 30 list of carcinogens in Europe and there are PVC plants around Europe where exposures are high.

Aflatoxin associated with mushroom farming is a potential liver carcinogen and this includes work in buildings with high levels of fungal and mould toxins (e.g. fumonisins). There are no occupational studies of aflatoxin exposure and there are few published data related to occupational exposure, but the exposed population and level of risk must be considered small. Consequently, there is no reason to regard this as a priority occupational carcinogen.

Polychlorinated biphenyls (PCBs) and biphenyls have been linked with cholangiosarcoma, a disease that is on the increase. However it is not clear whether this increase is real or is an artefact of changes in histological classification resulting in improved detection. The declining occupational exposure to PCBs must be taken into account, but there may be disposal issues when recycled plastics are ground to powder. Whether this should be classified as an IARC class 2A carcinogen is open to debate, but this will be difficult to resolve because there are few data on occupational exposure or effects in humans. The difficulty is that exposure to PCBs may occur in situations of exposure to many other agents such as dioxins, nitrosamines and dichloroethylene.

Dichloromethane used at high concentrations is also a risk factor for liver cancer. There is a weak association with trichloroethylene exposure, but this is based upon animal tests - hence their classification as IARC class 2B agents. The question is whether HSE needs to worry about these rare cancers and whether it has applied pressure to reduce exposure to these agents. Historically exposures were high but this situation has improved with use of better controls of exposure. Trichloroethylene is an IARC class 2A carcinogen used by the dry cleaning industry. Trichloroethane and perchloroethylene also are used but the risk of liver cancer associated with these agents is unclear and alcohol consumption represents an important potential confounding factor. There have been epidemiological studies related to high exposure situations but the data did not point to clear increases in most types of cancer and the populations exposed were small. The evidence demonstrates declining exposure on a par with vinyl chloride, and improved use of controls. Consequently, these agents need to be considered as low priority.

Oesophageal Cancers: The oesophagus is not a major site for cancer. This is not a signature cancer and the occupationally attributable risks are small compared with lung cancer. In relation to exposure to perchloroethylene the evidence for increased oesophageal cancer is weak and the data that are published have not generally been adjusted for the confounding effects of alcohol consumption. Exposure is usually of short duration with concentrations from ranging from 5 to 10ppm, which are below the occupational exposure limit, and it is difficult to envisage controlling exposure below this limit. However, these agents have neurotoxic effects, and this may justify further actions to control their use and associated exposure levels. With respect to current burden of cancers, the population of 'ever exposed' is likely to be high with estimates of up to 42,000 dry cleaners (and pressure cleaners) in GB. Cigarette smoke is recognised as a major confounding factor for oesophageal cancer.

Stomach Cancers: The data on inorganic lead are inconsistent with this being a stomach carcinogen, and recent data suggest that the trend in exposure is downward. Exposure to lead is carefully monitored as part of the control of lead at work (CLAW) regulations.. It may be worth commissioning a more up-to-date survey of exposures in British workers. With respect to exposure to the mixture of chemicals in paints, the exposed population is potentially high but the levels of exposure are not clear and the use of lead in paint has substantially declined. Some studies have suggested an increased risk of stomach cancer amongst painters, but these have not generally controlled well for confounding factors. Work in the rubber industry has been associated with increased risk, but this association is not firmly established, and if a causal relation does exist, then the number of attributable cases is likely to be small. Therefore, rubber should not be included on the priority list.

Cancers of the intestine: The one potential occupational risk factor is asbestos exposure, but the attributable number is low compared to respiratory mesothelioma, and the impact on the overall burden of cancer is likely to be very low.

Skin Cancer: One of the major work-related causal agents is solar radiation, for which there are very large numbers exposed. However, this needs to be set against the general population exposure, as well as the beneficial effects on Vitamin D production, from exposure to sunlight. Whilst these issues are difficult to disaggregate, this agent should be included as a priority because of the potentially large numbers exposed. Arsenic is a risk factor for skin cancer but the levels of exposure are usually very low.

With regard to coal tar pitch, the risk is for squamous cell carcinoma. The extent of the risk is uncertain, although the numbers of workers potentially exposed is high. Coal tar pitch is classified by NIOSH as an important carcinogen but there are many potentially confounding factors such as metal contaminants. The major sector associated with exposure is engineering. Mineral oil is not on the CAREX list, but historically this is an important exposure, particularly unrefined mineral oils used by car mechanics. Shale oil is unlikely to be a problem as the industry collapsed during the 1960s. Whilst for skin cancer exposure to soot is a risk factor, it is not clear whether this is due to the presence of PAHs or other carbon compounds and metals. The risk is for non-melanotic skin cancers. Fossil fuels may also need to be considered although one of the major agents, creosote, has been banned in the EU and cannot be considered a major risk for the future.

Brain and Central Nervous System Cancers: It has been suggested that epichlorhydrins are a risk for brain and CNS tumours, but the exposed population of workers in GB is very small and not well characterised. The evidence for a role of insecticides is also poor. With regard to petroleum products there is no consistent evidence of risk.. There has been speculation in recent times about the role of electromagnetic fields and mostly this research has been inconclusive. However, because of the high public profile this issue should be kept under review.

Points for Consideration / Actions by HSE:

- **Skin** was considered the major target organ for occupational cancers in this group.
- **Occupation** (e.g., painters) was considered the more relevant exposure metric rather than carcinogenic agent for assessing the attributable risk.
- **Occupational viral hepatitis:** As the numbers of cases are small, and appropriate intervention programs are in place, viral hepatitis should not be considered a priority in relation to secondary cancer risk, but HSE should consider monitoring this area.
- **Arsenic and skin cancer:** Given the low prevalence of exposures, arsenic must be considered of lower priority for this exercise.
- **Vinyl chloride and liver cancer:** Combustion of polyvinyl chloride can contribute to exposures, and there may be some value in monitoring levels close to incinerators sites and waste tipping sites, although the resultant exposures are not exclusively occupational.
- **Trichloroethylene and trichloroethane:** The evidence demonstrates declining exposure and there is no reason to regard this as a priority area.
- **Skin cancer and solar radiation:** This is one of the major hazards with large numbers exposed.
- **Electromagnetic fields and cancer:** Because of the high public profile of this issue it should be kept under review.

3.3.2 Selection of Methods and Data to Determine Attributable Fraction for Gastrointestinal, and Skins Cancers and Carcinogenic Processes.

Table 3.3. The priority list of agents and cancers

Cancer	Carcinogen
Non-melanoma skin	Solar radiation
Non-melanoma skin	Soots, tar, mineral oils

Non-Melanotic Skin Cancer - Solar Exposure: The range of exposure will be wide depending upon the nature of the occupation, but outdoor occupations have the highest levels of exposure. The GB cancer registrations record data only on a person's last occupation (if any) and not their lifetime occupations, and so it will not be easy to determine levels of previous exposure from this source. Potential confounding factors will include skin colour and levels of non-occupational exposure to sunlight. The categories of workers most exposed include those in the agricultural, forestry and construction sectors, but other workers such as postal staff are also exposed.

There are published data on exposure to sunlight in relation to occupational group but this data set does not include those working where sun exposure is limited. The risks will either have to be calculated using cancer registration data or using published case-control studies of skin cancer. There are published studies for the general population but not many investigations of occupational exposure. This analysis will need to take account of disability adjusted life years if the mortality data are used and there are published data on the proportion of cancer registrations by occupation.

Non-Melanotic Skin Cancer -Tars and Mineral Oils: Analysis of the attributable fraction should if possible be based upon case-control studies that provided information on the numbers exposed. Cohort studies are less likely to give generalisable estimates of exposure to these agents. If case-control studies are not available then longitudinal studies should be examined. Another complication is that effects on highly exposed people are likely to be diluted in larger populations of 'low exposed' individuals, but both will appear under the same job title. Motor mechanics are a relevant occupational group with excess mortality associated with oil use, and metal machining.

3.4 Haematopoietic & Soft Tissue Cancers

Members of group: Keith Palmer, Raymond Agius (*Chairs & Rapporteurs*); David Kriebel, Thomas Sorahan, John Cherrie, Eero Pukkala, Damien McElvenny, Alan Boobis

3.4.1 Selection of Priority Haematopoietic & Soft Tissue Cancers:

Leukaemia and non-Hodgkin's lymphoma were considered a difficult collection of cancers. It was decided to focus on the IARC class 1 and 2A agents. Concern was expressed about whether, for the class 2A compounds, there were good epidemiological data to support the use of published relative risk estimates. For the IARC class 2A compounds there are limited data on human exposure. Some of the uncertainty surrounding these compounds relates to the exact causative agent in each occupational circumstance. It was also decided to focus on cancer sites of interest and examine those agents that are relevant to these cancers.

Gamma, x-rays and ionising radiation are considered the most important workplace exposures that cause leukaemia. There is also some evidence that neutron radiation may be a risk for airline pilots and aircrew flying above 10 km, and cosmic radiation may be a factor. However, chronic lymphoid leukaemia and Hodgkin's lymphoma are not associated with exposure to these agents, and the most relevant solid cancers in the group are non-Hodgkin's lymphoma (NHL), and bone and soft tissue sarcomas. Of these, the non-Hodgkin's lymphomas are by far the most frequent. NHL represents ~4% of all cancers and is increasing in frequency, multiple myeloma accounts for ~1% of cancers. Bone cancers and sarcomas represent less than ~0.5% and are extremely rare.

Non-Hodgkin's lymphoma: There are many studies showing positive association with chemicals used in hairdressing, exposure to pesticides and to chlorinated hydrocarbons, trichloroethylene, tetrachloroethylene, 1,3-Butadiene, and possibly dioxins. Many of these agents have been classified using animal data, because the availability of human exposure and health effects data was limited. Of the occupational agents associated with NHL, one belongs to the IARC class 1 groups and 4 to the IARC class 2A group, which suggests that mainly class 2A agents are implicated. For dioxins there are limited human data to put these into the IARC class 1 group, but studies of exposure around incineration plants implicate this agent as a risk factor for NHL.

The problem with dioxin is that the exposure is systemic and there is no specific target organ, just an overall increase in the risk of cancers. Given the evidence of increasing incidence of NHL, case-controlled study to assess current exposures to dioxins may be justified, although these will take a long time to complete and would not have direct impact on this current exercise. Studies are being commissioned in other countries, which may report information relevant to exposures to dioxins in GB. There is limited availability of data on human exposure to dioxins, either in the CAREX database, or other relevant published studies, although some studies have examined exposure around waste incineration facilities. Consequently, the shape of the dose-response curves is unclear, i.e., whether it is linear or not. This is potentially a potent toxin and exposure to very low levels may be sufficient to cause cancer.

Trichlorethylene / Tetrachloroethylene – Leukaemia: The number of people occupationally exposed to these agents in GB has been estimated to be ~16,000 for trichlorethylene and ~120,000 for tetrachloroethylene. These have been classified as IARC class 2B agents and are risk factors for NHL but the likely exposure circumstances for both agents are very similar. Historically, exposure levels for trichlorethylene have been reported to be ~50–100ppm and for tetrachloroethylene ~20ppm. Ethylene dichloride has also been shown in animal based studies to be a potential cause of NHL, but this agent is an IARC class 2B agent and is being replaced in use.

These agents have been widely used in the dry cleaning sector but their use has been phased out by many businesses or put under better control by use of improved local exhaust ventilation systems. It is therefore likely that current exposure levels to these agents have fallen although the number of people exposed to low levels may remain high. Other sectors where these agents are used include light engineering and degreasing of machinery. An up-to-date systematic review was recommended with reference to the IARC list and classification. It was concluded that exposure to low levels of these agents may be common in industry but the magnitude of the relative risk was not clear.

Leukaemia and 1,3 Butadiene Exposure: HSE have collected a lot data regarding exposure to Butadiene exposure in the rubber and plastics industries. This agent is not listed amongst the top 30 carcinogenic agents in the CAREX list partly because it occurs mostly in certain chemical processes rather than as a widely dispersed agent. There is limited evidence about its carcinogenic effects in humans and these data suggest that the level of risk is quite small.

Leukaemia and insecticides: Agricultural workers are the main group exposed to pesticides, and for a number of pesticides there is a suggestion of an elevated risk of NHL. This has been

apparent in a number of studies and represents potentially a significant problem because of the size of the population who are exposed. However, the evidence for effect in humans is limited and general exposure to these agents is declining with time. Furthermore, the use of these agents is highly regulated in GB. Given the uncertainty it was suggested that this area should be subject to review, but HSE should take care not to give the impression that pesticides are an established cause of NHL.

If there is an increase in occupationally associated NHL but the causal factor(s) cannot yet be clearly identified, then HSE should put some effort into a long-term strategy to identify causative agents so that they can implement effective control measures. This may require a review of the literature both for occupational and environmental exposure, but it should be recognised that this would not directly help to deliver the 2010 occupational ill-health based targets.

To determine the burden of cancers associated with exposure to pesticides it will be necessary to identify published studies with relative risk estimates, and to take account of the changing pattern of exposure and current use of pesticides.

Leukaemia and benzene: Benzene has not generally been regarded as a potent cause of leukaemia but risk does increase with cumulative dose (Rinsky, 1989). In recent studies from Australia, benzene has been confirmed as a cause of leukaemia, although these studies have not been generally regarded as providing consistent evidence. Altogether the annual attributable number of leukaemias due to occupational exposure to benzene in GB is ~10-20, an estimate, which has been based upon large cohort, studies amongst oil distribution workers. It remains to be determined how many people are at risk from exposure to benzene in GB.

There are good data on benzene exposure amongst oil industry workforces in GB and whilst these demonstrate reducing exposure over time (in some cases to levels below current levels of detection) the suggestion has been made that a large cohort of workers may be exposed to low doses (below one part per million) with a demonstrable leukaemia risk. The CAREX database suggests ~300,000 exposed to benzene (e.g., truck drivers) because the cracking inside an engine generates benzene in the exhaust. If this pattern of cumulative exposure leads to a real increase in a risk then it suggests that there are potentially large numbers of people exposed to relevant low levels of benzene. However, this assumes a linear dose-response relationship for risk down to these low exposure concentrations. Co-exposures between benzene and 1,3 butadiene may also carry an increased risk for leukaemia.

Leukaemia and Ionising Radiation: The total number of cancers attributed to exposure to ionising radiation in GB is ~ 50-60 cases per year with leukaemias being a small proportion of these. The population of exposed workers in GB is estimated to be ~60,000 and is based upon the numbers registered as classified workers by the Health Protection Agency. However, these exposures are largely historical because of the improved use of controls in recent times and the decommissioning of nuclear plants. In addition to these workers, concern has been expressed about exposure to radiation amongst aircraft personnel. Studies of large cohorts of aircraft personnel (~50,000) suggest that the risk from radiation is small.

Leukaemia - Ethylene Oxide: It has been estimated that ~3800 people are occupationally exposed in GB. However, many uses of this chemical are being phased out. It is therefore difficult to predict what the effects of the current exposure profiles will be in future. Ethylene oxide is also found in natural substances but is not listed amongst the top 30 agents in the CAREX list. The mechanism of action as a carcinogen is considered improbable yet the substance has been reclassified as an IARC Class 1 substance.

Points for Consideration / Actions by HSE:

- **NHL and Dioxins:** For dioxins there are limited human data but studies of exposure around incineration plants implicate this agent as a risk factor for NHL and so case-control studies to assess current risk from dioxins may be justified, although NHL should not be considered overall a high priority for the HSE work.
- **Trichlorethylene and Tetrachloride:** An up-to-date systematic review was recommended with reference to the IARC list and classification.
- **Leukaemia and insecticides:** Given the current uncertainties it was suggested that this area should be subject to review.
- **Leukaemia and insecticides:** HSE should put some effort into a long-term strategy to identifying causative agents (if any) so that they can implement effective control measures. This may require a review of the literature both for occupational and environmental exposure but it should be recognised that this would not directly help to deliver the 2010 ill-health targets.
- **Leukaemia and benzene:** If low cumulative exposures carry a real increase in risk then there are potentially large numbers of people at risk, and so this area should be monitored closely.

3.4.2 Selection of methods and data to determine attributable fraction for Haematopoietic & Soft Tissue Cancers

Table 3.4. The priority list of agents and cancers

Cancer	Carcinogen
Leukaemia	Benzene
Leukaemia	Ionising Radiation
Leukaemia	1-3 Butadiene
Leukaemia	Ethylene oxide
Multiple cancers	TCDD

To determine the cancer burden associated with these agents, estimates of relative risks, levels of exposure, and number of subjects exposed will be required. Alternatively, it may be possible to repeat the Doll & Peto methodology as recently described by David Coggon (Coggon, 1999). However, concern was expressed that one approach may not be sufficient for every carcinogen and a hierarchy of approaches may be required.

Leukaemia - Benzene: This is an area of controversy, especially the proposal that potentially large numbers exposed to low concentrations of benzene are at increased risk of leukaemia. The consensus is that we do not know if there is a real excess risk, and more research is needed from a mechanistic viewpoint to determine whether the relationship between exposure and risk remains linear even at low concentrations. The toxicology shows possible associations with acute non-lymphatic leukaemia. There is a large amount of published data on cohort studies in selected industries such as the petrochemical and rubber processing sectors and there are good data on risks from moderate levels of exposure in GB.

One of the problems in interpreting the literature in this area is that, because of the occurrence of benzene in the general environment, a background of zero exposure does not exist. The exposure data are generally good for those exposed to high concentrations e.g., in the petroleum industry but large groups are potentially exposed to low levels and this need to be monitored carefully. Translated into the individual probability of getting leukaemia then the risk must be extraordinarily small. However, if HSE is looking at the whole country then this could add up

to a significant number of leukaemia cases. As there is an average latency period of ~10 years for leukaemia and benzene this will make it easier to collate these measurements.

One of the key steps in determining the attributable risk for these agents is how best to quantify the uncertainties around the dose-response curve at the lower exposure end. This may require assumptions to be made about the risk from exposure in terms of a range of values i.e., based upon different shapes of exposure curves and different distributions. These could be based upon exposure curves that have been determined by the US Environmental Protection Agency and would require a sensitivity analysis to be completed. Monte Carlo simulations could be used to determine the best fit to the data and the error around the different distributions. It was not thought that confounders represent a major problem because it has been established that the relative risk for smoking and leukaemia is small. Other potential confounding factors may include co-exposure to butadiene and alcohol consumption, but there is insufficient experimental evidence to tell us about the level of interaction between these confounders.

Leukaemia - Ionising Radiation: Data on numbers occupationally exposed to radiation can be derived from the registers of classified workers, and the exposure profile of these workers may be determined from CIDI. However, the GB cohort studies could be compared with predictions from the Health Protection Agency using data derived mainly from exposure to the Japanese atomic bomb survivors. In addition, to data from the main industries in GB, relevant data from other sectors where exposure occurs, should be included, such as ongoing studies of air cabin crews. This data should be applied to standard internationally agreed risk estimates and would not necessarily rely on epidemiological data but would require estimates based upon hygiene measurements, e.g., altitude of flight, time of flight and sun spot activity.

Leukaemia and 1, 3 Butadiene: HSE has carried out a risk assessment of this compound as part of the Existing Substances Regulations programme and there is a lot information collected on levels of exposure for the rubber industry and for people handling motor fuel. In addition to this many published studies have reported on exposure levels for different sectors of industry as well as on the effects of confounding factors. There are no reliable relative risk estimates even at high levels of exposure to butadiene, and not all of these studies contain data of high quality. In general, the data suggest a rather low relative risk from exposure to this agent. A critical analysis of the strength of the existing epidemiological data is required to determine the relevant current exposure levels that apply in GB and whether there are specific differences between sectors of industry.

Multiple Cancers - TCDD: There are problems with the data on exposure to TCDD particularly the epidemiology studies, which point to a non-linear dose-response curve that may be a result of underlying non-genotoxic effects of these chemicals. The status of TCDD as an IARC Group 1 is based on limited human data but the supportive animal data are more robust. However, for the expected occupational exposures, the relative risk estimates appear inconsistent and not very large, although many people are exposed to low levels. The number of people in total exposed to TCDD is similar to those exposed to 1,3 butadiene, but a complication is the prevalence of non-occupational exposure, which is high and represents a public health issue. Policy makers will need to decide whether to take a central (or a high end) estimate of the number exposed. A provisional estimate of the number of cases attributable to TCDD exposure lies between 0-500. Given the large uncertainty, it may be necessary to adopt a precautionary approach and reduce occupational exposure.

Leukaemia and Ethylene Oxide: There are large studies that have examined exposure to this agent. One particular study examined 3,600 workers with elevated exposure levels. The occupations most likely to be associated with exposure were in the health sector related to sterilisation of instruments and possibly in workers involved in fumigation. Some data should be available for GB sites, but are likely to represent historical rather than present exposure patterns. A review of the epidemiology was recommended which would assess the value of taking a risk versus an exposure-based approach to estimating the attributable number of cancers. Unlike the

other agents selected, the risk of exposure to leukaemia was not so clear and the epidemiological studies that have been completed have suggested a low risk following exposure to ethylene oxide. The consensus was that this agent should be a low priority given the background of falling exposures within GB.

Leukaemia and non-ionising radiation: Whilst this is an area of controversy (particularly electromagnetic fields and cancer), given the large numbers of people potentially exposed and the likely lag period between exposure and onset of disease, non-ionising radiation should be included in the list of a priority agents. It was concluded that the systematic literature reviews considered by the HPA's advisory group on non-ionising radiation should be relied upon. The possible risks of brain cancer were also noted.

Points for Consideration / Actions by HSE:

- **Leukaemia and 1, 3 Butadiene:** A critical analysis of the strength of the existing epidemiological data is required to determine the relevant exposure levels in GB and where these currently occur.
- **Cancers and TCDD:** It may be necessary to place an upper boundary on the estimated number of attributable cases as a precautionary approach to reducing occupational exposure.
- **Leukaemia and non-ionising radiation:** There should be a systematic literature review to assess whether this is a relevant risk for leukaemia.
- **Leukaemia and non-ionising radiation:** Given the large numbers of people potentially exposed it was recommended that non-ionising radiation be included in the list of priority agents.

4.0 Discussion & Conclusions (Chaired by Kyle Steenland)

One source of data that will be important for this study is the decennial supplement. Southampton University are preparing for the next supplement together with HSE and the Office of National Statistics. It was also recommended that data should be drawn from the CAREX database and from national Job Exposure Matrix databases, although these will need to be adjusted for GB. Some concerns were expressed about the inconsistency of the data held in these databases and new systematic reviews of case-control studies may be required to pull together studies from different countries. The consistency of these different data sources is important and, if there are enough European studies, these could be used to determine the risk related to similar work tasks. Systematic reviews are required and should prioritise data sets from within GB.

The question of whether the linear exposure model is best should also be addressed, particularly if there are limited data. For some agents, a linear dose-response may not be applicable. For some compounds that are not genotoxic, a sensitivity analysis may be needed and a reconstruction of the likely exposure range. The analysis will need to focus on those agents where the occupational cancer exposure link is well established, so that current (and potentially future) burdens can be determined. For those agents where the relationship is non-linear, a different approach may be needed such as disaggregating the data. One of the key factors in determining the attributable risk will be the duration of exposure as this is generally a more important determinant of risk than peak exposure. However, it may not be possible to complete these reviews within the time frame for this current exercise.

The difficulty is accounting for all cancers in terms of known occupational carcinogens. Whilst most carcinogens were discovered a long time ago, the number of new agents being recognised has gone down. This may indicate that there are new types of 'undiscovered' carcinogens that may be different in nature to those that we currently recognise or simply that not enough time has elapsed for them to be properly evaluated. We have not included or considered all possible agents in this list and this reflects a publication bias. A systematic approach is needed for exposure measurements to see what the future burden is likely to be and this should include a better understanding of the risk to the individual. This will require objective measures. HSE already carries out monitoring activity for a range of industries, and personal exposure monitoring or preferably biological monitoring are ideally suited methods to fill in the gaps for 'missing' priority agents. Biological monitoring has to be linked to exposure measurements, and we need more up-to-date information particularly regarding exposure in small to medium sized enterprises (SMEs). It is important that this exposure monitoring data is stored in easily accessible databases. Plans have been developed to provide a web-enabled version of the NEDB. Resources should also be put into the completing areas of NEDB where the data sets are incomplete.

Points for Consideration / Actions by HSE:

- Systematic reviews of case-control studies may be required to pull together studies from different countries to focus on those agents where the occupational cancer exposure link is well established so that current (and potentially future) burdens can be determined. However, there may be problems completing these reviews within the time frame for this current exercise.
- The presence of new yet 'undiscovered' carcinogens must be considered.
- A systematic approach is needed for collection of exposure measurements to determine what the future burden of cancer is likely to be, and a better understanding of the risk to the individual. HSE should continue to make use of personal exposure monitoring and biological monitoring to fill in the gaps for 'missing' priority agents.
- The use of biological monitoring linked to exposure measurements should be considered to gather more data on exposure in small to medium-sized enterprises.
- Exposure data need to be stored in easily accessible databases.
- Resources should also be put into the completing areas of NEDB where the data sets are incomplete.

5.0 Recommendations and Conclusions

5.1 General conclusions:

- It is appropriate and feasible to update Doll and Peto's 1981 estimate of the proportion of cancer attributable to occupational causes for GB.
- In doing this, the uncertainties in the science underpinning estimates of attributable fractions must be made clear.
- In planning preventive strategies, a balance must be drawn between the need to reduce unacceptably high risks in individuals and the need to minimise the excess burden of disease at a population level.
- Insofar as the aim of future interventions is to reduce the overall burden of occupational cancer, there will be a limit to what can be achieved by controlling only high exposures, since for many occupational carcinogens the majority of attributable cases arise from low exposures.
- Consideration should be given to estimating impacts on disability-adjusted life-years as well as attributable numbers of cancers.

5.2 Methodology – general strategies

- Possible methods for estimating the excess of a cancer that is attributable to occupation are;
 - Direct estimation from representative population-based case-control studies that have assessed risks from relevant exposures or in relevant occupations.
 - Application of exposure-response relationships derived from one source (e.g. meta-analysis of cohort studies in a systematic review) to data on the population distribution of exposures derived from a different source (e.g. occupational hygiene surveys).
 - Extrapolation from estimates of attributable numbers for another disease caused by the same hazardous agent, with assumptions about the exposure-response relationships for the two diseases.
 - Application of attributable fractions estimated from studies in other countries to data on cancer incidence in GB.
- The optimal method of estimation will differ by cancer and carcinogen.
- Assessment of the overall burden of occupational cancer should allow for the possibility that some occupational carcinogens may yet be unrecognised. Thus, as well as estimates based on 'definite' carcinogens, upper bounds for attributable numbers should be derived, taking into account 'possible' carcinogens.
- Assessments based on the excess incidence of cancer in selected occupational groups may be more vulnerable to unrecognised confounding effects than those based on risk estimates for specific carcinogenic agents.
- However, a consistent excess of cancer in an occupational group could reflect effects of one or more unrecognised occupational carcinogens, and should not be ignored.

- A good rule of thumb for estimating the number of workers ‘ever-exposed’ to an occupational carcinogen is to multiply the number currently exposed by a factor of four.
- Care is needed in the use of risk estimates for ‘ever’ versus ‘never’ exposure to a carcinogen, since levels of exposure in ‘ever exposed’ groups may vary importantly from one study to another.

5.3 Methodology regarding dose-response relationships

- Duration of exposure needs to be taken into account as well as level of exposure.
- Linear dose-response relationships should not be assumed without question.
- Toxicological data on dose-response patterns may be useful if there are insufficient human data on a dose-response relationship.

5.4 Impact of effect modifiers

- In some cases, effect modifiers may have an important impact on attributable numbers. Thus, it will be important to assess trends in non-occupational risk factors such as smoking that might interact with carcinogens of interest.

5.5 Methodology regarding areas of uncertainty and confounding factors

- Characterising uncertainties is as important as obtaining central estimates. Estimates of risk should include an assessment of the potential impact of bias and confounding factors as well as chance.
- Where empirical data are lacking, it may in some circumstances be necessary to apply expert judgement.

5.6 Sources of information

- CAREX and the Finnish job-exposure matrix (FINJEM) are useful sources of exposure data, but these would need to be supplemented with data from the NEDB. Current work looking at trends in exposure should be exploited, as well as hygiene surveys commissioned by HSE and other Existing Substances Reviews, EH64 data, and data in the scientific literature.
- Relevant data on the size of occupational groups may be available from national censuses.
- The ONS decennial supplements on occupational mortality (including the next such analysis, which is currently being planned) may provide useful information on rates of fatal cancers by occupational group.

5.7 Developing our knowledge of occupational cancers in women

- We need to be aware of possible occupational hazards of cancer that are specific to women, and which have not been investigated as extensively as many other suspected carcinogens (e.g. the link between shift work and breast cancer).
- There was disagreement about whether to take account of indirect effects of occupation on risk of cancer (e.g. altered risk of breast cancer because of differences in the reproductive behaviour of working women).

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7.0 Appendices

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