Medical Research Council

Institute for Environment and Health

IEH report on

VARIABILITY AND SUSCEPTIBILITY IN HUMAN RESPONSE TO OCCUPATIONAL EXPOSURE TO CHEMICALS IN THE UK

2002 REPORT R13

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DR GIORGIO ARESINI

It is with great sadness that we record the death of workshop participant Dr Giorgio Aresini in Luxembourg on 19 August 2001. He was a dedicated advocate for the health of all working people within the European Union and will be very much missed by his many friends and colleagues.

Contents

Executive summary

Work patterns in the UK have changed over the last 20 years and are continuing to do so. Employees change jobs more often and no longer think in terms of 'a job for life'. Such changing work patterns may potentially result in exposure of workers to a variety of chemicals over varying periods of time rather than the same chemicals over a working life.

The UK Health and Safety Executive commissioned the MRC Institute for Environment and Health to organise a workshop to examine the existing state of knowledge of variability and susceptibility in the response of the UK workforce to occupational exposure to chemicals. A range of factors were taken into account, starting with the changing demography of the UK workforce in terms of gender, ethnicity and age, together with its biological variability for inherent factors such as physiology, xenobiotic metabolism and genetic polymorphism. Superimposed on this are acquired lifestyle factors and characteristics such as obesity, medication, existing health status and the use of tobacco and alcohol. Also considered was the possibility that an older population will, in future, make up a greater proportion of the UK workforce.

It was concluded that variability and susceptibility in the working population is unlikely to be significantly different from that in the general adult population.

The following recommendations were made to improve knowledge about susceptibility and variability within the working population and improve approaches to the regulation of occupational chemicals.

- Human data from existing databases could be used to validate a physiologically-based pharmacokinetic model, which could be used to predict the chemical kinetics for pathways without suitable probe substrates or *in vivo* data.
- Observational studies on variability in response to routine exposure to certain chemicals in the workplace should be conducted by recruiting individuals working in environments where their exposure and response can be readily monitored.

- Data (for example, blood parameter measurements, liver function tests, blood levels of a chemical over time) from the National Poisons Information Service should be examined to compare the range of toxic responses to a particular chemical for a range of individuals, to obtain some indication of the variability in response.
- Biological markers, such as FEV_1, could potentially be used to examine the variability of lung function response to the same chemical exposure in a group of workers over time.
- As animal data are not appropriate to investigate variation in human toxicodynamics, the development of *in vitro* tests using human tissue samples should be considered to provide data to help bridge the knowledge gap in this area.
- Body weight default values should be reviewed by determining the current range of body weights for male and female workers of various age groups. Up-to-date information is available in the literature but needs to be compiled and analysed. Ranges of body weight and their use in risk assessment need to be considered.
- The prevalence of asthma and atopy in the working population should be monitored by means of a longitudinal investigation to determine whether the increase of 10–15% and 40–50%, respectively, that has been predicted is real and not a result of improved diagnosis and increased reporting.
- Lung function should be examined in older (currently post-retirement) age groups to determine whether this would be an issue in an ageing workforce. The existing norms are based largely on extrapolation from younger populations and may not be accurate for older age groups.
- Existing occupational data should be reviewed, targeting, initially, workers exposed to organic solvents, to investigate the interaction between alcohol and exposure to chemicals.
- A biomarker for long-term alcohol intake levels could be developed to assist the study of potential interactions between alcohol and chemicals in workers.
- A survey should be conducted to determine the range and amount of prescribed and recreational drugs currently being used by the UK working population.

- Existing animal data should be reviewed to determine whether, in general, pregnant animals are more sensitive to chemicals than their non-pregnant counterparts.
- There has been a suggestion that occupational exposure to a range of commonly used organic solvents may result in central nervous system dysfunction post-retirement. In order to explore this further it may be appropriate to conduct a follow-up study of retired solvent-exposed workers for any evidence of neurobehavioural or other nervous system-related changes.

Historical note

Although this report brings together contemporary science and thoughts on what is known about human variability, individual susceptibility and the way in which lifestyle or other personal factors may affect the response to chemicals in the occupational context, it is important to note that such questions have exercised those concerned with ill-health caused by industrial chemicals for many years. As examples, the following two quotations from the eminent and pioneering occupational physician Alice Hamilton (1929)* are offered.

"*Individual Susceptibility* — Idiosyncrasy was understood by the Greeks to mean so peculiar a mixture of body fluids that the introduction of a drug would cause an abnormal reaction, either over-great or over-slight. Not only might the reaction to a drug be abnormally marked but a reagent which caused no injury to a normal person might set up symptoms in those with an idiosyncrasy, and this idiosyncrasy was held to be inborn, often hereditary. We no longer talk of a peculiar mixture of body fluids, but we are no nearer than the Greeks to an explanation of the familiar phenomenon of one person reacting to rag-weed pollen, another developing hives after eating strawberries, another asthma because of the proximity of a horse. Nor can we explain why there is such a difference in the susceptibility of different individuals to the same industrial poison. All we know is that two men will be working at the lead pot, the one will be taken and the other left; two women will be spreading benzene cement, the one will be taken and the other left."

"*Alcoholic Drink* — The influence of alcohol on industrial poisoning is important, although not so important as is generally supposed by employers, managers and foremen. I believe there is no form of industrial intoxication in industry, from lead to carbon disulphid, which I have not heard attributed to alcohol, no matter what the clinical picture might be. Even physicians often assure me that the lead, or mercury, or anilin, or naphtha poisoning, about which I am inquiring, never occurs in sober men, only in alcoholics; yet if they would copy the careful

* Hamilton, A (1929) *Industrial Poisons in the United States*, New York, Macmillan

methods used by Tanquerel des Planches, a century ago, they could easily convince themselves as he did, that many men who lead sober, righteous and godly lives, suffer as severely as the drunkards."

These two examples simply illustrate the point that variability and susceptibility were recognised even if not fully understood. Nowadays, we have explanations for some, but not all, such phenomena.

1 General introduction

Harmful effects of chemicals to either working populations or those in the population who might be incidentally exposed to chemical substances used in the workplace are prevented or ameliorated by the use of a range of control strategies and tactics. This has been the case in all industrialised countries for many years and includes the use of occupational exposure limits (OELs) in the case of airborne substances, biological monitoring guidance values, specific prohibitions of either certain substances or persons related to specific circumstances, and other forms of control including codes of practice and targeted guidance. The adoption of such preventive measures has carried the implication that the degree of protection afforded in the UK and elsewhere relates to "nearly all" the potentially exposed workforce, but usually without any further definition of "nearly all". In general, this pragmatic approach has served reasonably well and specific control or advice has been provided to "susceptible groups" on an *ad hoc* basis when particular problems have been identified. However, in recent years there have been numerous developments in knowledge that would enable the provision of better information, both qualitative and perhaps quantitative, in relation to toxicant exposure and ensuing risk. Coupled with this, there have been changes in the nature of work in the UK, particularly a reduction in the numbers of the workforce involved in traditional manufacturing industries, such as shipbuilding, coalmining, iron and steel making and heavy engineering, where exposure to hazardous substances was more prevalent than in the newer service-based industries. Other changes in demography, such as the predicted need for the workforce to continue working beyond the currently accepted retirement ages, make it necessary to re-evaluate what is meant by "nearly all".

The UK Health and Safety Executive (HSE) contracted the Institute for Environment and Health (IEH) to organise a workshop on the existing state of knowledge of variability and susceptibility in the response of the UK workforce

to occupational exposure to chemicals. A major objective of the workshop was to identify uncertainties and important data gaps that could be addressed by research. Thus Government scientists and policy-makers, who have the responsibility for the protection of both the workforce and those who may be affected by work activities, may be able to use the best science to underpin their regulatory activities with a greater degree of confidence in relation to subgroups and individuals and, just as importantly, be able to highlight their uncertainties and any important data gaps that could be filled with targeted research.

At this workshop, convened in February 2001, experts in occupational and environmental health, clinical pharmacology, toxicology, risk assessment and policy-making presented papers reviewing current knowledge of human variability and susceptibility, particularly in relationship to the UK, and identified the factors that are important in determining individual risk or risk from particular chemical substances.

A range of factors were taken into account, starting with the changing demography of the UK workforce in terms of gender, ethnicity and age, together with its biological variability for inherent factors such as physiology, xenobiotic metabolism and genetic polymorphism. Superimposed on this are acquired lifestyle factors such as obesity, medication, existing health status and the use of tobacco and alcohol. Also considered was the fact that an older population might, in future, make up a greater proportion of the UK workforce. This makes it more important to consider the functional reserve of vital organs in relation to normal decline in organ function and general fitness with age and how this might interplay with chemical exposure. It is important to note that, although addressed during the workshop, a number of areas were not explored in depth as either they were too extensive, or would form the basis for other workshops or activities. These included a detailed examination of exposure patterns in the workplace and the direct effect of chemical substances on the developing fetus.

This report summarises the presentations and discussions that took place at the workshop. Short papers summarising the presentations given by the invited experts are included in Section 2 and a summary of the subsequent discussions at the workshop and recommendations for the future are presented in Sections 3 and 4.

2 Variability and susceptibility in human response to occupational exposure to chemicals in the UK

2.1 BACKGROUND TO THE HEALTH AND SAFETY EXECUTIVE'S NEEDS: UK WORKFORCE DEMOGRAPHY — NOW AND IN 10 YEARS

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2.1.1 INTRODUCTION

Risk assessment of occupational chemicals is an essential step in protecting the health of workers and consumers. Judgements are made by comparing a measure of dose or exposure with an estimation of human response. Consideration of these judgements in the context of a particular scenario provides an estimate, often crude, of risk and controls deemed to be appropriate are then advocated. This can be a contentious process: in reality information is often limited and good human data are rarely available. The interventions implemented may, for example, be the use of tools such as exposure limits at the workplace, or conditions on

supply as in pesticides approval, or information conveyed through classification and labelling systems. Many of these interventions are developed with reference to a concept of a 'normal' individual — normal, that is, in terms of physiology, health, behaviour, intelligence, skills etc — and are assumed to protect all or nearly all of the working population.

Protection requires practical and sensible controls, proportionate to the risk and meeting public concerns. It should take into account the characteristics of the exposed population, be undertaken at the earliest opportunity, be monitored for effectiveness and adjusted in the light of experience.

Underestimating the risk to at least some members of the exposed population could have serious consequences, but high levels of control are expensive. Hence, it is necessary to ensure that the margins of safety used in establishing risk management standards are appropriately set. Conventions already exist for setting margins of safety but the basis on which they are founded needs to be reassessed. Standards must be justifiable in terms of protecting, but not overprotecting, all the exposed population. The use of much lower safety margins in the occupational setting (Fairhurst, 1995) than the 100-fold used in some circumstances needs to be questioned. A recent report (Risk Assessment and Toxicology Steering Committee, 1999a) has queried whether sufficient is known about human diversity to ensure that there is enough information to protect, within reason, the whole working population. There is a need to determine whether a realistic set of worst-case criteria can be specified alongside what might be regarded as normal, thereby allowing standards to be set to protect the whole working population, or whether this would be likely to lead to such a high degree of control as to be unworkable in practice.

2.1.2 RISK ASSESSMENT STRATEGIES

There has, for some years, been concern within UK Government departments and the Research Councils over the many aspects of risk assessment, especially of chemicals. An initiative was begun in 1995 under the Risk Assessment and Toxicology Steering Committee (a subgroup of the Interdepartmental Liaison

Group on Risk Assessment) aimed at stimulating the development of new, improved approaches to the assessment of risks to human health from chemicals. A series of workshops has been held and a number of reports produced (Risk Assessment and Toxicology Steering Committee, 1999a–f). Of particular relevance here is the workshop on 'Risk Assessment Strategies in Relation to Population Subgroups' (Risk Assessment and Toxicology Steering Committee, 1999c). The members of this workshop were charged to:

- examine the relevance and scientific basis of current extrapolation procedures (used in chemical risk assessment) and the ways in which they account for population variability;
- suggest how these procedures could be improved;
- consider whether special risk assessment provision should be made for certain population subgroups; and
- make recommendations regarding the research required in order to obtain better underlying information and to develop improved methods of risk assessment.

The following recommendations were made.

- Further research is needed to increase knowledge on the response of specific subpopulations to toxicological insult, in order to determine whether, on the basis of scientific evidence, additional uncertainty factors may be needed to allow for the presence of such subgroups in a population.
- Further work should be undertaken on interindividual variations in toxicokinetic and toxicodynamic parameters, in particular on the inherent variability within the human population due to genetic factors affecting the metabolism of chemicals. In particular, *in vitro* screens should be developed further to determine the metabolic pathways for chemicals and their regulation in humans, in order to estimate the size of population subgroups that have a genetic deficiency in metabolism.
- Further information is need on the interaction of nutritional status, nutrition and response to chemicals.
- Research is needed on variations in immune response and on the importance of immunotoxicological end-points, in order to increase understanding of immunologically mediated susceptibility and how this might be addressed in risk assessment.

The factors that are taken into account in judging human risk are long established through convention, custom and practice. Undoubtedly they have served the working population well, but their continuing validity needs to be assessed. More knowledge is needed of the diversity of the human population. At the very best the factors need to be challenged in relation to changed ideas of what constitutes occupationally related ill-health, and changes within the structure of employment and the working population.

Concern is frequently expressed over cases of human ill-health postulated as being linked to chemical exposure, especially when the sufferer is a child. It needs to be determined whether there are population groupings, for example children or the elderly, at particular risk that can now be identified and factored into risk assessments. It is possible that lessons might be learnt from, for example, pharmaceutical research. This pooling of information was a recommendation of the 1997 workshop (Risk Assessment and Toxicology Steering Committee, 1999c). Definition of a small group of model individuals, representing significant points on the scale of diversity, that can be used to benchmark the risk assessment process might represent a way forward.

2.1.3 CHANGES IN THE WORKING POPULATION

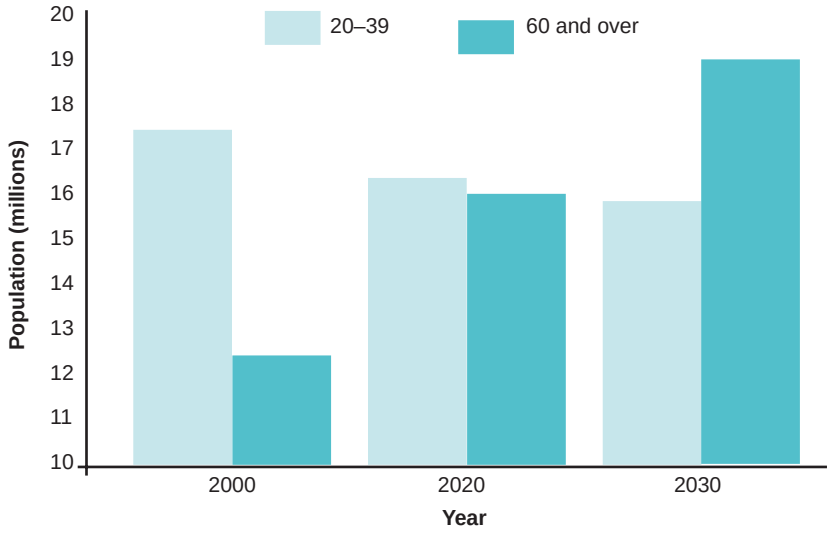
Society is also in a period of marked change. Heavy industry has much declined, being replaced by employment in the service sector, and much of the ill-health seen today is a legacy of this old employment. There is a strong movement throughout western Europe to an information-based economy. This will bring ill-health concerns of its own, particularly stress (ILO, 2000)*, but also a change in tolerance of the consequences of manufacturing industry.

The UK working population is at the beginning of a substantial change due to many years of low birth rate (below replacement level) and the ageing of those born in the post-war baby boom. Financial and social pressures are also likely to increase the number of over-60s in the active workforce, with among these a greater proportion of women. A projection was made of this change some years

* ILO (2000) *Globalizing Europe. Decent Work in the Information Economy* (Report of the Sixth European Regional Meeting, Geneva, Vol 1), Geneva, Switzerland, International Labour Office, available at http://www.ilo.org

ago (Figure 2.1). On current trends there will be more women in the labour force than men by 2020 (DTI, 2000)[a].

Figure 2.1.1 The shifting age balance of the UK population: 20–39 year olds compared with those aged 60 and over



Data from GAD (1998)[b]

Across Europe the trend is for higher levels of female employment, more part-time working and changes in the structure of employment (more contracted staff). This raises questions on the relevance of conventions based upon a 40 year working life, the response to chemical exposure of an ageing workforce, possible interactions with medication and the burden of long latency disease. Societal drivers towards maintaining a longer and rewarding working life are strong and meeting the challenges of an ageing population is a priority. "Our older population is increasingly healthy, has much experience to offer and, on the whole, cannot be financially supported by the state as they live longer, leading us to the

[a] DTI (2000) *Labour, Leisure and Learning Taskforce* (Foresight Ageing Population Panel Report), London, UK, Department of Trade & Industry, available at http://www.foresight.gov.uk
[b] GAD (1998) *Population Projections and Life Expectancy*, London, UK, Government Actuary's Department, available at http://www.gad.gov.uk

conclusion that it is in the UK's interest to make better use of its older workers by encouraging them to continue to work beyond the current state retirement age" (DTI, 2000). A precondition of meeting this goal must be fitness to work.

Broadly the aim of the workshop was to take forward some of these considerations, so that HSE would be better placed to judge where strengths and weaknesses lie, and what might be targeted for further work, probably through commissioned research or international collaboration.

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Risk Assessment and Toxicology Steering Committee (1999e) *Physiologically-based Pharmacokinetic Modelling: A Potential Tool for Use in Risk Assessment,* Leicester, UK, MRC Institute for Environment and Health

Risk Assessment and Toxicology Steering Committee (1999f) *From Risk Assessment to Risk Management: Dealing with Uncertainty,* Leicester, UK, MRC Institute for Environment and Health

2.2 SUMMARY OF THE 'SELF REPORTED WORKING CONDITIONS IN 1995' SURVEY

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2.2.1 BACKGROUND

As part of a continuing programme to develop its information on work-related illness, the Health and Safety Executive (HSE) commissioned a series of questions in the August and October 1995 Omnibus Surveys of the Office for National Statistics. A sample of 3209 adults employed in the previous 10 years were asked questions about certain conditions they might have experienced at work.

This took place in parallel with the 'Self-reported Work-related Illness Survey' in 1995 (Jones *et al.,* 1998), which asked adults in a representative sample of households in England and Wales whether they felt they had suffered from any illness or condition caused or made worse by their work. This paper details the findings of the study on working conditions and is based on the replies of the 2230 individuals who were employed when interviewed. The figures and tables included here are taken from that study (Jones *et al.,* 1997).

The principal purpose of the study was to identify job characteristics that might be associated with the occurrence of work-related illness by comparing these findings with those of the 'Self-reported Work-related Illness Survey' (Jones *et al.,* 1998). However, the findings of the study are of interest in their own right, as a baseline for comparison between occupations, as a baseline against which future trends might be assessed, and as background information for other studies of work-related illness.

It is important to be clear about the nature of this information. The aspects of working life that were surveyed were chosen for their potential influence on employees' health and well-being. But it must be understood that the prevalence of these work characteristics is *not* a measure of the health of people at work. For example, the fact that 29% of respondents said that they always or nearly always had to work to tight deadlines is not in itself 'good' or 'bad'. Working under pressure is a component of overall work pressures which, in certain circumstances, can lead to health problems, but the reported prevalence itself does not indicate the level of such problems or even whether they exist.

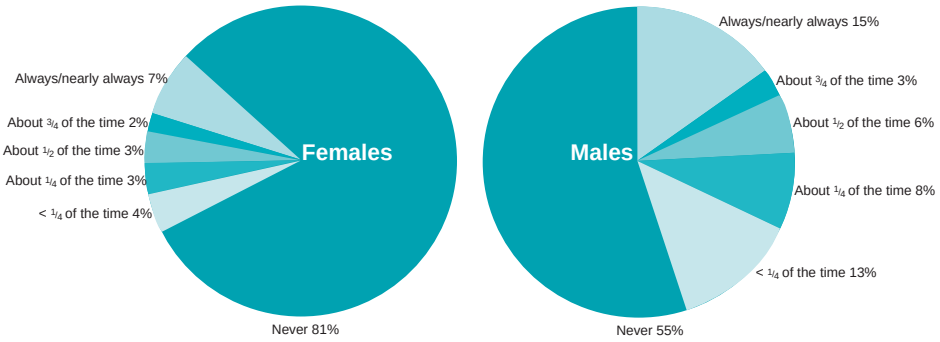
2.2.2 QUESTIONS ON EXPOSURE

The questions of interest in the present context are those that relate to exposure to 'harmful substances'. Self-reports on exposure are open to variable interpretation. Whether breathing fumes or handling substances is a potential risk to health depends on the nature and degree of exposure; some substances are harmless at low levels. Individuals' views on whether a given substance is harmful may be inaccurate and this survey provides no information on the existence of controls within the workplace that can eliminate the health risk involved in these situations. Nevertheless some indication of the distribution across the workforce of potentially harmful exposures can be derived from these data, which are summarised below.

BREATHING FUMES, DUST OR OTHER HARMFUL SUBSTANCES

The prevalence of male current workers sometimes being exposed to breathing fumes, dusts or other harmful substances in their job (45%, CI 42–48%) was more than double the prevalence for females (19%, CI 16–22%). This difference occurred in all age groups. Almost one-third (CI 29–35%) of males and 15% (CI 12–17%) of females reported being exposed for at least one-quarter of their working time (Figure 2.2.1, and Table C1 in Jones *et al.,* 1997).

Figure 2.2.1 How often current workers were exposed to breathing fumes, dust or other harmful substances in their job



Data from Office for National Statistics Omnibus Survey, August/October 1995

Male-dominated, manual occupational groups showed a higher risk of sometimes being exposed to breathing fumes, dust or other harmful substances than other occupational groups (Table 2.2.1). In particular, construction (86%, CI 76–97%), metal processing (77%, CI 67–86%), other processing (70%, CI 60–81%), and farming, fishing and forestry (68%, CI 52–84%) had rates which were more than double the average for all occupational groups. Electrical processing (60%, CI 39–79%), materials moving and storing (54%, CI 33–72%), and road transport operatives (52%, CI 39–65%) also had significantly raised rates.

Table 2.2.1 Percentage of current workers who were ever exposed to breathing fumes, dusts and other harmful substances in their job, by occupational group and sex, and overall occupational relative risk

Occupational group[a]	Number of respondents		% responding 'yes'[b]			Relative risk[c]
	Males	Females	Males	Females	Persons	Persons
Construction	60	0	86	NA	86	2.66 ++
Metal processing	95	8	80	*47*	77	2.35 ++
Other processing	84	20	72	*63*	70	2.15 ++
Farming, fishing & forestry	39	11	*78*	*33*	68	2.09 ++
Electrical processing	34	0	*60*	NA	*60*	1.80 ++
Other transport & machinery operatives	18	0	*57*	NA	*57*	1.70
Materials moving & storing	33	3	*55*	*40*	*54*	1.62 ++
Road transport operatives	84	1	52	*0*	52	1.59 ++
Hair & beauty	8	16	*19*	*61*	*47*	1.53
Textile processing	6	33	*50*	*48*	*48*	1.49
Repetitive assembly, inspection	25	19	*56*	*33*	*46*	1.39
Security & protective services	40	7	*42*	*29*	*40*	1.24
Managerial	147	60	41	26	36	1.11
Science & engineering	115	16	35	*43*	36	1.10
All occupations	**1170**	**1050**	**45**	**19**	**33**	**1.00**
Other personal services	10	15	*45*	*14*	*27*	0.86
Other education & welfare	21	48	*25*	*27*	26	0.80
Catering	16	58	*17*	26	*24*	0.75
Nursing	4	72	*0*	25	24	0.73
Cleaners	14	62	*18*	24	23	0.69
Teaching	27	58	*23*	17	19	0.58 -
Professional & related supporting management	90	65	17	11	14	0.46 --
Selling	69	84	24	7	14	0.44 --
Literary, artistic & sports	17	16	*12*	*13*	*13*	0.37 -
Clerical	68	184	19	9	12	0.37 --
Secretarial	7	93	*21*	7	8	0.25 --
Care workers	6	71	*33*	5	8	0.27 --

Data from Office for National Statistics Omnibus Survey, Aug/Oct 1995

NA, not applicable

[a] Occupational groups 'miscellaneous' and 'missing' have been excluded from this table

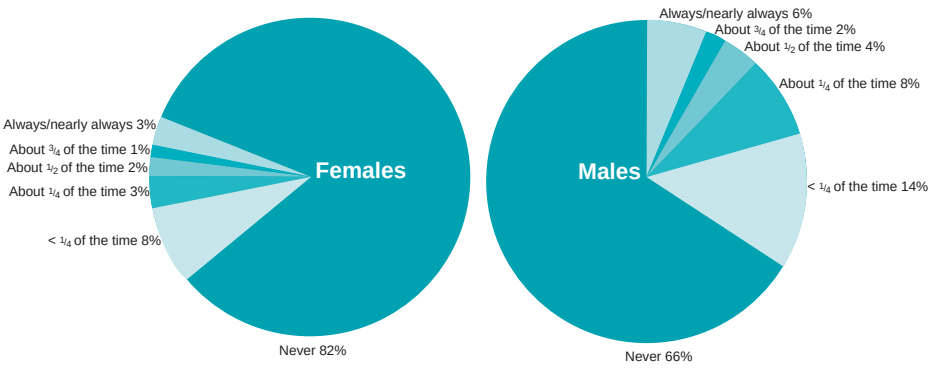
[b] Percentages in italics are based on fewer than 50 sample cases

[c] ++/-- Relative risk significantly above or below average ($p < 0.1$); +/- relative risk significantly above or below average ($p < 0.05$)

HANDLING OR TOUCHING HARMFUL SUBSTANCES OR MATERIALS

A higher proportion of males (33%, CI 30–37%) than females (18%, CI 15–21%) said their job sometimes involved the handling or touching of harmful substances or materials. The prevalence was higher for males in all age groups. One-fifth (CI 17–22%) of males and one-tenth (CI 8–13%) of females reported being exposed for at least one-quarter of their working time (Figure 2.2.2, and Table C1 in Jones *et al.,* 1997).

Figure 2.2.2 How often current workers were required to handle or touch harmful substances or materials in their job



Data from Office for National Statistics Omnibus Survey, August/October 1995

Nearly one-fifth (CI 16–20%) of respondents indicated that their current job sometimes exposed them to breathing fumes, dusts or other harmful substances, or required them to handle or touch harmful substances or materials (Jones *et al*., 1997). A further 59% (CI 56–61%) of respondents reported that their job *never* exposed them to breathing fumes, dust or other harmful substances or required them to handle or touch harmful substances or materials.

Table 2.2.2 Percentage of current workers who were ever required to handle or touch harmful substances or materials in their job, by occupational group and sex, and overall occupational relative risk

Occupational group[a]	Number of respondents		% responding 'yes'[b]			Relative risk[c]
	Males	Females	Males	Females	Persons	Persons
Hair & beauty	8	16	*75*	*71*	*72*	2.86 ++
Farming, fishing & forestry	39	11	*66*	*48*	62	2.36 ++
Nursing	4	72	*28*	64	62	2.36 ++
Metal processing	95	8	63	*27*	60	2.29 ++
Construction	60	0	56	NA	56	2.10 ++
Other processing	84	20	59	*34*	54	2.05 ++
Electrical processing	34	0	*48*	NA	*48*	1.79 ++
Other transport & machinery operatives	18	0	*43*	NA	*43*	1.69
Security & protective services	40	7	*38*	*57*	*41*	1.54 +
Science & engineering	115	16	38	*40*	38	1.45 ++
Cleaners	14	62	*44*	30	33	1.25
Repetitive assembly, inspection	25	19	*40*	*20*	*31*	1.21
All occupations	**1170**	**1050**	**33**	**18**	**26**	**1.00**
Other education & welfare	21	48	*35*	*22*	26	0.99
Materials moving & storing	32	3	*27*	*0*	*25*	0.98
Other personal services	10	15	*30*	*21*	*25*	0.91
Catering	16	59	*20*	22	22	0.81
Teaching	27	58	*31*	17	22	0.81
Care workers	6	71	*17*	19	19	0.74
Managerial	147	60	24	8	19	0.72 -
Road transport operatives	84	1	16	*100*	17	0.67
Selling	69	84	18	10	13	0.50 --
Literary, artistic & sports	17	16	*19*	*3*	*11*	0.46
Professional & related supporting management	90	65	9	6	8	0.29 --
Clerical	68	184	7	5	5	0.21 --
Textile processing	6	33	*33*	*0*	*5*	0.20 --
Secretarial	7	93	*0*	0	0	0.00 --

Data from Office for National Statistics Omnibus Survey, Aug/Oct 1995
NA, not applicable
[a] Occupational groups 'miscellaneous' and 'missing' have been excluded from this table
[b] Percentages in italics are based on fewer than 50 sample cases
[c] ++/-- Relative risk significantly above or below average ($p < 0.1$); +/- relative risk significantly above or below average ($p < 0.05$)

The hair and beauty occupational group (Table 2.2.2) showed the highest proportion of sometimes being exposed to handling or touching harmful substances (72%, CI 51–93%), nearly three times the average for all occupations. The rate among nurses was more than double the average (62%, CI 49–75%), and the remaining occupational groups with significantly raised rates were manual and male dominated: farming, fishing and forestry (62%, CI 46–78%); metal processing (60%, CI 49–72%); construction (56%, CI 40–70%); other processing (54%, CI 42–65%); security and protective services (41%, CI 24–57%); electrical processing (48%, CI 27–67%) and science and engineering (38%, CI 28–48%).

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2.3 UK WORKFORCE EXPOSURE TO CHEMICALS — NOW AND IN 10 YEARS

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2.3.1 INTRODUCTION

The term 'chemical agent' is taken as defined in Council Directive 98/24/EC (EC, 1998) to mean "…any chemical element or compound, on its own or admixed, as it occurs in the natural state or as produced, used or released, including release as waste, by any work activity, whether or not produced intentionally and whether or not placed on the market". In the UK, this will be the basis for defining substances hazardous to health under the Control of Substances Hazardous to Health (COSHH) Regulations 2002, and includes naturally occurring materials (e.g. flour, wood, minerals), dusts and mixtures, as well as chemicals and preparations listed in Part 1 of the Chemicals (Hazard Information and Packaging for Supply) Regulations (HMSO, 1994) as very toxic, toxic, harmful, corrosive or irritant.

Reviews and references on assessment methodologies, measurement and modelling of occupational exposure can be found in numerous publications, such as Harris (1993), the European Commission Technical Guidance Document (European Commission, 1996) in support of the Risk Assessment Directives (EEC, 1967, 1993), and the European Foundation booklet on occupational exposure databases (Rajan *et al.*, l996).

2.3.2 SOURCES OF DATA ON OCCUPATIONAL EXPOSURE TO CHEMICALS

Smith & Glass (1992) have suggested that 41 organisations across Europe hold databases on occupational exposure, while Vinzents *et al.* (1994) referred to one million measurements held in five databases. The largest source of data in the UK is the Health and Safety Executive (HSE) National Occupational Exposure Database (NEDB) set up in 1986 (Burns & Beaumont, 1989).

The NEDB data are not in the public domain, although Tickner (2001) has provided the following breakdown: 80 000 exposure samples gathered since 1986, 12 000 abstracts of all occupational hygiene visit reports prepared by HSE staff since 1983 and 20 000 asbestos exposure samples taken between 1972 and 1986. Some data have been gathered from industrial sources, although most were generated by HSE Inspectors and are mainly associated with a limited range of specific processes or hazards. Some data on specific substances have been published but overall trends on exposures are not available and there are difficulties in assessing the quality and comparability of data. Prior to 1996, there were no standards for data entry and supporting information in European exposure databases. Although Rajan *et al.* (1996) proposed core information and data fields to improve the quality of exposure measurements held in European Union (EU) National databases, interpretation of data prior to 1996 can be problematical.

There are just over 100 000 substances in the European Inventory of Existing Commercial Substances (EINECS)*, of which 30 000 are estimated to be currently produced and used in volumes of above one tonne in the UK (European Commission, 1996). This does not include mixtures or naturally occurring substances. Even with an estimated 100 000 entries spanning more than 10 years, the NEDB provides only limited information on the current exposures of the 28 million employees (CBI, 2000) in the UK.

* SilverPlatter (2001) *EINECS-Plus: European Inventory of Existing Commercial Substances*, London, SilverPlatter Information Ltd, available [January 2001] at http://www.silverplatter.com

Data from larger companies and industrial associations are valuable in providing an insight into historical exposures in particular industrial sectors; for example CONCAWE (2000) and Bell *et al*. (1995) have reviewed measurements and estimates of benzene exposure in the oil industry. These studies demonstrate the difficulty in obtaining and comparing data, even in a major industry-wide study. In comparison, many sectors of industry have little or no access to the resources and expertise required for valid occupational exposure assessment. Good quality data collection is also expensive — this author (R Alesbury) estimates that the cost per sample for a valid estimate and interpretation of personal exposure is in the order of £300–£500. In a comparable area, Slovak, in Rushton and Betts (1997), provides an insight into the resources and expertise necessary fully to characterise exposure to ionising radiation in the nuclear industry.

Efforts at modelling occupational exposure using the EASE (Estimation and Assessment of Substance Exposure) model (Friar *et al*., 2001) have met with some success, although exposures have been calculated for only a comparatively small number of tasks and are dependent on reference measurements to validate calculation parameters. Cherrie *et al*. (2001) have proposed a theoretical model of human inhalation and dermal exposure and its implications for measurement but acknowledge that "the absence of an explicitly articulated theory hampers accurate assessment of human exposure". Modelled data are a poor substitute for good quality, validated occupational exposure measurements. In order of declining preference as a means of assessing occupational exposure are measured, analogous, surrogate and modelled data.

A comprehensive understanding of inhalation exposures across the UK would require valid data from a representative cross section of activities and substances. Current data, measured or modelled, do not meet this need. In particular, there are major gaps in information on large sectors of commerce and industry, particularly small and medium-sized enterprises. Furthermore, the traditional focus on inhalation exposure in the practice of occupational hygiene and the absence of consistent methodologies and models for assessing dermal exposure mean that there are limited data on most occupational exposures by dermal contact (Jackson, 1999; Schneider *et al*., 1999) or ingestion.

2.3.3 CHANGES IN EXPOSURE OF THE WORKFORCE

The views of a selection of occupational hygiene, medical and toxicology professionals with experience of industry, trade unions and HSE were canvassed by the use of a multiple choice questionnaire. Although these views have been instrumental in developing this paper, the data are insufficient to warrant statistical analysis. The following predictions are therefore the personal and, by definition, largely unsubstantiated, views of the author.

Workforce exposure is dependent on many factors, including: timing (duration and intervals between tasks), where people work, the tasks carried out, personal habits and practice, the range of hazardous substances that may be encountered and the effectiveness of any control measures. In the following sections an analysis is made of how these might affect trends in occupational exposure over the next 10 years.

Demographic change will continue to be reflected in the distribution by age and gender of the working population. The trend to greater flexibility and structural changes in employment will increase the range of jobs and tasks that many individuals encounter in their working life. With increased variability in tasks comes the potential for an increase in the number of chemicals to which any one individual is exposed. With more frequent job changes, the learning of new tasks, lack of familiarity with operating practices and low skill level could also act to increase peak or short-term exposures, although improved attention to task design and employee competency may help to mitigate these effects.

Currently 4.2 million people (15% of the total workforce) are in manufacturing employment, representing a 16% reduction since 1990 (CBI, 2000). The last 20 years have seen a major restructuring of UK business and the decline of heavy industry with large workforces. Many traditional industries have disappeared or been reduced in significance in terms of the number of plants and people in employment. Those traditional industries that remain are more automated and have fewer employees. Over the same period, total employment has increased, primarily in service industries and in small and medium-sized enterprises (CBI, 2000). This change in the industrial landscape has dramatically reduced the

numbers employed in industries associated with classic industrial diseases (e.g. cotton mills, coke ovens, mining, etc). In other heavy industries, such as steel, where employment fell from 271 000 in 1978 to 48 000 in 1998 (Hansard, 2000)*, automation has helped reduce exposure (to dust, fumes and gases) of the remaining employees in the industry. In contrast, tasks in construction or maintenance and those requiring craft skills (e.g. manual welding, woodwork, baking) have changed less. Although further change in heavy and traditional industry may be anticipated, this will impact on a much smaller proportion of the population in employment, as restructuring and the drive to automation and improved technology continue to reduce the number of people employed in manufacturing. With automation and the trend to greater enclosure and segregation of chemicals from the workforce, exposure of production workers may be anticipated to decline further. Conversely, maintenance of more complex plant may result in greater need to break containment, with consequent opportunities for contact and exposure to a wide range of chemical agents.

Overall, exposures in large manufacturing organisations will almost certainly continue to decline, as these organisations are subjected to restructuring and/or investment and new technology. These larger companies are also more likely to benefit from access to professional occupational hygienists with the necessary skills and competence to assess risks from chemical agents, design appropriate control measures and advise on the changes necessary to reduce exposure.

2.3.4 REGULATIONS AND CONTROL MEASURES

For people working in small companies and service industries there are practical difficulties in accessing the skills necessary to understand the complexities of current regulations and the science and technology associated with the assessment of health risks and their control. Exposures to chemical agents in these smaller organisations, in which an increasing proportion of the workforce are employed, are also most likely to be associated with traditional craft or skilled activities, where the prospect for change from new technology and automation is limited.

* Hansard (2000) *Employment Changes 1948–98, by Industry*, available [September 2001] at http://www.parliament.the-stationery-office.co.uk/pa/ld199900/ldhansrd/

Control custom and practice for craft or maintenance activities has evolved little and the practical effectiveness of commonly used control measures, such as ventilation and personal protection, is often poor. In the printing industry for example, 170 000 people are employed in more than 12 000 companies — an average of 14 per company (Livesley & Rushton, 2000). Although larger organisations in the industry may benefit from new technology, traditional machines used in smaller companies have a long life and are often second-hand, offering the prospect of only slow improvement from new technology. With slow penetration of technological change, limited awareness and low priority devoted to health issues at work, the prospect for any significant reduction in exposures in craft occupations or small companies is minimal.

New molecules are being developed but generally require massive investment in research and development, most notably in industries such as pharmaceuticals and fine chemicals. These are generally well-controlled processes involving small numbers of employees in comparison with the total population in work. Substitutes, for example solvents in paints, are also changing the nature of some operations, in some cases reducing the nature and extent of exposure but having limited effect overall on many traditional or craft activities. In comparison with the 30 000 chemicals in common use (CEC, 2000), the overall impact of new molecules and regulatory intentions to ban or restrict use will have minimal impact overall on UK workforce exposures. Substitution is also not without problems, with the potential to move from a well understood material to a less well researched molecule, which may subsequently be found to be equally or even more hazardous.

Voluntary initiatives, such as the Chemical Industry Responsible Care Programme (CIA, 1989*), Education of Safety Representatives by Trade Unions and partnerships with HSE are of value in spreading information and good practice. The production of *COSHH Essentials* (HSE, 1999a) is a good example of a partnership between industry, unions and regulators, providing a simple but effective tool to help users prevent or control exposure. Even so, the overwhelming number of small companies makes it unrealistic to expect anything other than a token improvement without a corresponding step change in awareness and approach to regulation and regulatory compliance.

* Chemical Industries Association (1989) *Responsible Care*, available [September 2001] at http://www.cia.org.uk/industry/care.htm

Regulatory pressures should theoretically drive improvement. The new COSHH regulations, enacting the Chemical Agents Directive (EC, 1998), are intended to improve the control of exposures to chemicals at work. However, surveys by HSE on awareness of COSHH across industry (HSE, 1998) and on the use of occupational exposure limits show only limited understanding and awareness of current regulatory requirements in many, particularly smaller, companies. As the new COSHH regulations will be longer, more complex and more prescriptive than COSHH 1999 (HMSO, 1999), it is unrealistic to expect a significant improvement.

Increasing scientific research on chemical hazards, the adoption of the precautionary principle and the trend to extend protection to more susceptible populations continue to add pressure for reduced occupational exposure limits. However, with low levels of general awareness, an increasing proportion of the population working in smaller organisations and limited availability and access to occupational hygiene expertise, changes in limit values will have minimal impact on overall UK workforce exposure.

With few exceptions, regulatory pressure has probably not been the major contributor to reducing occupational exposures to chemicals in the past few decades, and there is little optimism that it will in future. Without simplification of the overall regulatory burden and more focus on the needs of small organisations, it is difficult to envisage a major change over the next 10 years in small to medium-sized enterprises and in craft activities.

2.3.5 FUTURE TRENDS IN WORKFORCE EXPOSURE

There is no reliable way of assessing current exposure for most of the UK workforce, nor are there exposure data to allow reliable estimation of future trends. Using circumstantial information, demographic trends and informed opinion, an estimate of future trends has been made.

In future, there will be fewer production workers but, with increasing regulatory pressure, improved technology and automation, there will be continued decreases in time-weighted average exposures for those working for major employers.

However, these decreases will only apply to a small and declining proportion of the workforce. Perversely, automation and enclosure may serve to increase the potential number and intensity of peak/short-term exposures and dermal exposures occurring during maintenance work in the newer plants.

Small and medium-sized enterprises account for an increasing proportion of the workforce and there is little reason to anticipate major changes in exposures in these organisations over the next 10 years. Continued changes in the overall pattern and nature of employment are certain, although major structural changes in traditional industries over recent years leave limited scope for a further step change in exposure levels. Of more significance will be the impact of demographic changes and changes of employment, leading to greater diversity of exposures for any one individual. The rate of change in small organisations handling chemicals, and traditional craft activities has been less pronounced and there are limited prospects that the situation will change significantly in the next 10 years without a fundamental change in the approach to regulation, health risk management and enforcement activity.

Overall, there will be a continued change in industry and commerce affecting patterns of exposure but little reason to anticipate a marked improvement in inhalation or dermal exposure levels for the overall working population.

2.3.6 A WAY FORWARD?

Securing Health Together (HSE, 2000b) sets out a forward programme with ambitious targets to reduce occupational illness. This identifies a number of important issues but the challenges, particularly to improve awareness and compliance in smaller enterprises, are understated. A step change in exposures to chemical agents in the UK over the next 10 years will be dependent on the effectiveness of measures to reduce exposure in craft and trade activities, in particular, those in small and medium-sized organisations. The current regulatory approach to control of exposure to chemicals at work has its roots in a system designed for employment concentrated in large organisations. In the 21st century a radically different approach is needed: emphasis on regulatory simplicity; improved access to basic occupational hygiene expertise; and more, high profile enforcement. Although public awareness of health hazards has increased

dramatically in recent years, there needs to be a concerted effort to raise understanding of risk.

The development of *COSHH Essentials* (HSE, 1999a), with a focus on simplicity and impact, gives some cause for optimism. This approach can be customised to suit particular trades or processes, with specific guidance on control in a particular industry, for example printing (HSE, 2000a), or industrial sector. The adoption of simple standards of competence (BIOH, 1998a) in the *Approved Code of Practice* for asbestos regulations (HSE, 1999b) recognises the role of basic but affordable levels of training and competence. This could be easily extended to training of employee and trade union safety representatives, and health and safety specialists, using other modular programmes offered by BIOH (1998b).

A reduction in occupational exposures in the future can be anticipated only if a radical move to simplicity and effectiveness takes precedence over, and resources from, the trend to regulatory complexity.

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2.4 UK OCCUPATIONAL HEALTH SURVEILLANCE SCHEMES: WHAT DO THEY TELL US?

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No single source of information is available in Great Britain on the nature and full extent of occupational and work-related ill-health. The policy of the Health and Safety Executive (HSE) is to make the fullest use of a range of sources, and develop new ones where necessary. Different sources of information usually give varying sized estimates of the extent of work-related disease, reflecting differences in severity and the extent to which cases have been confirmed as work related. This is illustrated by a comparison of the following major sources.

- The Industrial Injuries Scheme (IIS), operated by the Benefits Agency on behalf of the Department of Social Security (DSS) gives compensation for specified 'prescribed diseases' which are conditions whose occupational cause is well established. Cases are individually confirmed by medical examination and checking of the work history. (In the following text 'assessed cases' means cases assessed under this scheme as having disability rated at 1% or greater.)

- Voluntary surveillance schemes for the reporting of occupational disorders are coordinated by the University of Manchester with HSE funding. They include schemes known as SWORD, EPIDERM, OPRA and others which have been added under the umbrella scheme known as ODIN (Occupational Disease Intelligence Network). These schemes count new cases that are caused by work in the opinion of the specialist doctor who sees them. Statistics are compiled for occupational respiratory, skin, hearing, and musculoskeletal disorders, infections, and psychological disorders (including stress), based on reports from these schemes. It should be noted that not all cases of occupational disease will be seen by participating specialists, and that coverage by occupational physicians, who form a major component of ODIN, varies considerably according to industry or type of employer.
- Household surveys yield estimates of the number of people who say that they have conditions that they think have been caused or made worse by work. Such surveys obviously depend on lay people's perceptions of medical matters, but such perceptions are of interest in their own right, and responses can be validated in various ways. Surveys are the only way in which any estimate can be made of the large volume of work-related disease that may not be seen or recognised by doctors. HSE has carried out two surveys of self-reported work-related illness, in 1990 (Hodgson *et al.,* 1993) and 1995 (Jones *et al.,* 1998), referred to hereafter as SWI90 and SWI95.
- Death certificates are useful for monitoring the most serious forms of some types of occupational lung disease, including cancers, but are of limited use for other conditions.

The following accounts, based on information from *Health and Safety Statistics 1999–2000* (Health and Safety Commission, 2000), illustrate how these different surveillance sources can be brought to bear on two important categories of chemical-related occupational illness: asthma and dermatitis.

2.4.1 OCCUPATIONAL ASTHMA

Indications of the total incidence of occupational asthma, and some idea of the relative importance of the different sensitising agents, can be obtained from the reports of new cases seen by chest physicians reporting to the SWORD project and occupational physicians reporting to the OPRA project (referred to jointly as

SWORD/OPRA for brevity), and from new Disablement Benefit assessments under IIS (Box 2.4.1). Occupational asthma has a much more rapid onset than, for example, pneumoconiosis and so it is likely that new assessments or cases reported to SWORD/OPRA reflect current or recent working conditions rather than those of the past. However, there is some delay in newly diagnosed cases being assessed and claims can be made retrospectively within 10 years of exposure to prescribed agents.

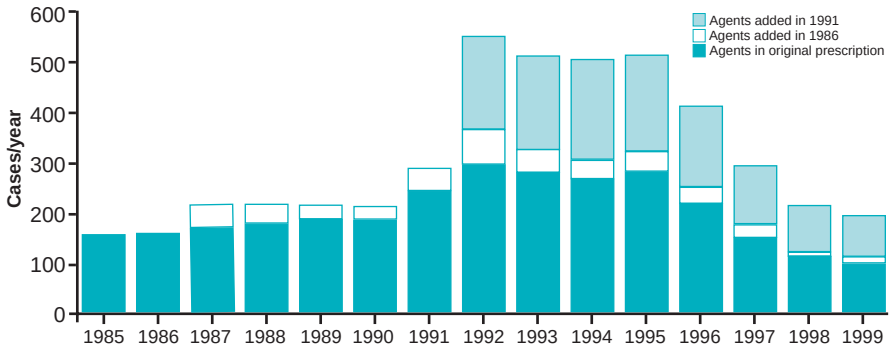
Box 2.4.1 Trends in the incidence of occupational asthma

- An estimated 1118 cases of occupational asthma were seen for the first time by occupational and chest physicians who reported to the SWORD/OPRA project in Great Britain in 1999, around 4 cases per 100 000 workers per year. After allowing for under-reporting and cases never seen by chest or occupational physicians, the true incidence is likely to be considerably higher, perhaps 20 or more cases per 100 000 workers.
- Trends in occupational asthma are difficult to assess from the available data sources, but there appears to have been little change in annual incidence over the 10 years from 1990 to 1999; at most there may have been a small fall from 1997 to 1999.
- Isocyanates were the most commonly cited agents for both SWORD/OPRA and IIS cases in 1999, with flour/grain being the second most commonly incriminated agent group for both sources.
- Over half of all SWORD/OPRA occupational asthma cases in 1998/99 came from the manufacturing sector. The occupation with the highest incidence rate of occupational asthma was spray painters, where the estimated rate based on SWORD/OPRA data in 1998/99 was 118 cases per 100 000 workers per year.
- The 1995 Self-reported Work-Related Illness Survey estimated that there were 151 000 people in the working population with asthma symptoms which they believed to be work related.

Data from Health and Safety Commission (1998), Jones *et al.* (1998); Health and Safety Commission (2000)

Summary data for the number of occupational asthma cases qualifying for Disablement Benefit are given in Figure 2.4.1. Total numbers have risen as further agents have been added to the original (1982) prescription in 1986 and 1991. The numbers of assessed cases fell considerably in 1997, 1998 and 1999. At least part of the fall in 1997 may have been connected with changes in DSS data collection procedures, which took effect from that year. However, the number of cases fell again in 1998 and still further in 1999, suggesting a genuine fall in the numbers seeking compensation.

Figure 2.4.1 Occupational asthma: Disablement benefit cases, by year



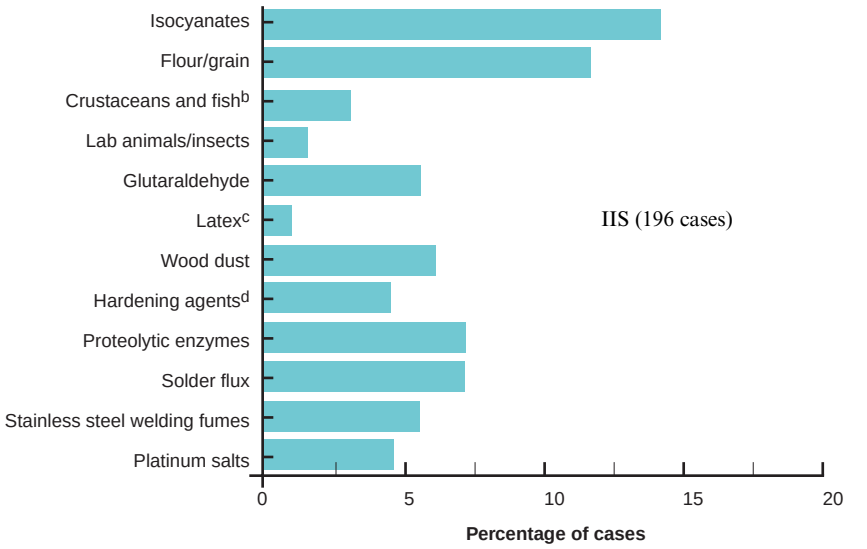
Between 1996 and 1999, SWORD/OPRA recorded more than three times as many cases of occupational asthma in Great Britain (3987) as were assessed under IIS (1126). The latter is known to exclude certain categories of sufferer (see above discussion of sources). The SWORD/OPRA figures themselves are also affected by under-reporting. Many cases will not be reported, including those not seen by chest physicians (who tend to see only the more serious cases), those occurring in individuals who do not have access to occupational physicians, and those that are simply never diagnosed.

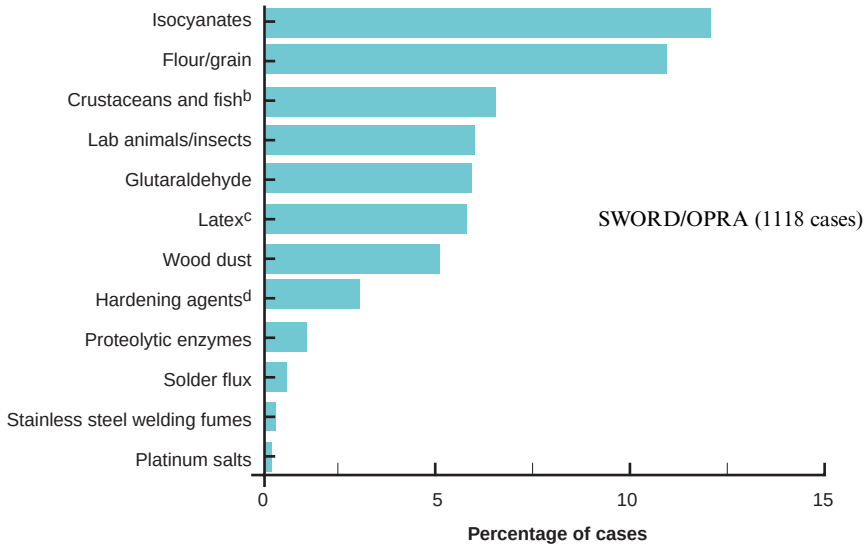
Previous reviews of the data (Health and Safety Commission, 1998) have estimated that the true incidence of occupational asthma diagnosed by consultant physicians may be as high as 1500–2000 or 6–8 cases per 100 000 workers, per year. As most cases of occupational respiratory disease are not seen by a consultant physician, the total incidence of the disease may be several times higher still, perhaps as many as 20 or more cases per 100 000.

From 1997 to 1999, occupational asthma numbers reported to SWORD/OPRA fluctuated around an average rate of almost 1000 cases per year, which is similar to the number seen over the preceding three years. However, the proportion of total SWORD/OPRA reports involving occupational asthma fell slightly, from around 31% in 1994–1996, to 26% in 1997–1999. While this percentage will, of course, be affected by changes in trends for other diagnostic categories as well as asthma it may, taken alongside the small fall in numbers of IIS cases, suggest a slight fall in the incidence of occupational asthma from 1997 to 1999.

In terms of the agents incriminated in occupational asthma cases, the SWORD/OPRA schemes tend generally to record a wider range of agents and to pick up more quickly an increase in prominence for particular agents than does IIS. Figure 2.4.2 shows the percentage of IIS and SWORD/OPRA cases attributable to the specific agent categories that accounted for 30 or more SWORD/OPRA cases, or five or more disablement cases in 1999 (excluding the open category). It should be noted that, in some cases, the agent categories for the SWORD/OPRA data are approximations to the DSS categories. For example, the category 'hardening agents' for SWORD/OPRA consists entirely of those reports attributed to epoxy resins while the SWORD/OPRA category 'crustaceans and fish' is clearly wider then the DSS category 'crustaceans'. Both sources recorded isocyanates and flour/grain as the top two agent categories, which between them accounted for 23% of SWORD/OPRA cases and 26% of IIS cases. Looking further down the list of the most prominent agents, SWORD/OPRA recorded a higher percentage of cases attributable to the two agent categories 'crustaceans and fish' and 'laboratory animals and insects' (each 6% of the total, compared with 3% and 2%, respectively, for comparable DSS categories). Conversely, the agent categories 'proteolytic enzymes' and 'soldering flux' each accounted for 7% of all IIS cases, compared with less than 1% for the SWORD/OPRA data. This analysis seems consistent with the observation that SWORD/OPRA better represents the incidence of respiratory disease among women, as the agents which SWORD/OPRA show as being more prominent are in occupations with a higher proportion of female employees, such as laboratory technicians (Ross *et al.*, 1998). Interestingly, in 1999 both sources showed latex as accounting for 6% of all cases; in previous years, SWORD/OPRA had shown a much higher proportion than the IIS figures.

Figure 2.4.2 Cases of occupational asthma recorded by the Department of Social Security (DSS) Industrial Injuries Scheme (IIS) and SWORD/OPRA, by causative agent[a], 1999





[a] DSS prescribed agents plus latex
Agents on chart account for 71% of DSS cases and 57% of SWORD cases
[b] Includes fish for SWORD data only
[c] Latex is included in DSS 'open category'
[d] Only 'Epoxy resin hardening agents' feature in this category

Table 2.4.1 shows the numbers of new cases of occupational asthma seen by the physicians participating in SWORD/OPRA in 1998 and 1999, analysed by occupation. Rates per 100 000 workers are given for the two schemes added together in the final column. It should be borne in mind when interpreting these figures that access to an occupational physician will vary considerably from one industry or occupation to another and that chest physicians will mainly see the more serious cases, so that the occupational distribution of SWORD/OPRA cases may differ from the true picture. Bearing this in mind, the analysis shows that the three occupations with the highest rates of occupational asthma were coach painters and other spray painters, bakers and flour confectioners, and welding trades.

2.4.2 DERMATITIS AND SKIN DISORDERS

The most widely based estimate of the prevalence of work-related skin disease comes from SWI95. The report provides an estimated prevalence of self-reported work-related skin disease of 66 000 cases (95% CI 43 000–88 000) for Great Britain.

The best source of information on the incidence of work-related skin disease, and contact dermatitis in particular, is from the EPIDERM and OPRA voluntary surveillance schemes (Cherry *et al.*, 2000) covering cases seen by dermatologists and occupational physicians, respectively (Box 2.4.2).

Since, however, the figures from EPIDERM/OPRA are subject to variability due to sampling, a better source of information on trends in occupational dermatitis is data from DSS disablement benefit cases. Figure 2.4.3 shows the number of cases assessed as having more than 1% disability for the years 1987/88–1998/99. The number of cases with such disability has shown a continuing steady decline from the early 1990s, falling from 433 in 1990/91 to 220 in 1998/99, the latest year for which data are available. There were around 4500 cases of dermatitis reported to EPIDERM and OPRA in 1996, and in the years 1997–1999 there were around 4100, 4500 and 4800 cases, respectively. Although trends are difficult to predict from the surveillance schemes, the indications are that the estimated annual number of cases of skin disease seen by reporters is approaching 5000.

Table 2.4.1 Occupational asthma: Estimated number of cases reported by chest and occupational physicians to SWORD/OPRA and estimate of rates per 100 000 workers per year, by occupation: 1998–1999, Great Britain

Occupation[a]	Chest physicians		Occupational physicians[b]		Chest and occupational physicians[b]	
	Average estimated cases 1998–1999	Rate per 100 000 workers per year	Average estimated cases 1998–1999	Rate per 100 000 workers per year	Average estimated cases 1998–1999	Rate per 100 000 workers per year
Managers and Administrators	**17**	**0**	0	0	**17**	**0**
Professional	**45**	**2**	30	1	**75**	**3**
Medical Practitioners	10	7	12	8	**22**	**15**
Associate Professional and Technical	**47**	**2**	**85**	**3**	**132**	**5**
Laboratory Technicians	8	8	0	0	**8**	**8**
Nurses	**24**	**5**	42	8	**66**	**13**
Clerical and Secretarial	15	0	24	1	**39**	**1**
Craft and Related	**176**	**6**	**127**	**4**	**302**	**10**
Welding Trades	**41**	**42**	8	8	**49**	**50**
Bakers, Flour Confectioners	**12**	**34**	13	36	**24**	**70**
Coach Painters, Other Spray Painters	**29**	**81**	13	37	**42**	**118**
Personal and Protective Service	**18**	**1**	18	1	**36**	**1**
Sales	1	0	6	0	7	0
Plant and Machine Operatives	**159**	**6**	**83**	**3**	**242**	**10**
Other Food, Drink Process Operatives n.e.c.	**29**	**24**	18	15	**47**	**40**
Chemical Plant Operatives	**22**	**33**	19	29	**41**	**62**
Assemblers (vehicles and metal goods)	**6**	**8**	12	15	**18**	**23**
Packers, Bottlers, Canners, Fillers	**15**	**7**	1	0	**15**	**8**
Other Occupations	**53**	**3**	54	3	**107**	**5**
Missing Occupations	2	NA	6	NA	8	NA
All Occupations	**530**	**2**	**432**	**2**	**962**	4

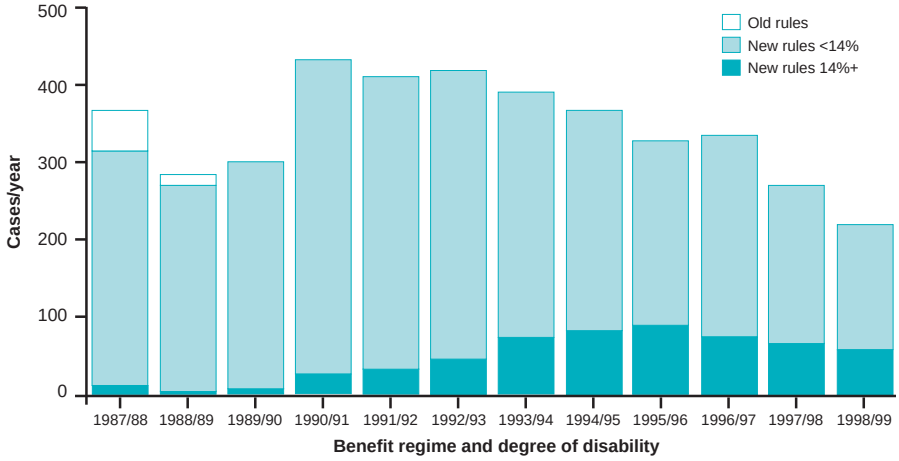
Where estimated cases and rates are based on fewer than 10 actual cases, figures are shown in light type
NA, not applicable; n.e.c. not elsewhere classified
[a] Standard Occupational Classification (SOC; Office of Population, Censuses and Surveys, 1990), 90 minor groups with 10 or more actual cases reported across both schemes in 1998–1999 are shown
[b] Some rates based on or including OPRA reports are liable to be artificially low where they refer to occupations or industries where few workers are under the care of occupational physicians

Box 2.4.2 Trends in the incidence of dermatitis and skin disorders

- Occupational skin disease is common, with SWI95 estimating the prevalence of self-reported work-related skin disease in Great Britain as 66 000. Approximately two-thirds of these cases were of dermatitis or eczema.
- Over the period 1998–1999 there were an estimated approximately 4500 cases of work-related skin disease seen each year by specialist physicians. Approximately 80% of these cases were of contact dermatitis.
- The annual number of cases of occupational dermatitis assessed as having some degree of disablement continues to fall, from around 400 in the early 1990s to around 200 in the late 1990s. Trends in incidence from the EPIDERM and OPRA surveillance schemes are difficult to assess, but the indications are that the estimated annual number of cases seen by reporters may be approaching 5000 per year.
- The occupations estimated to be at highest risk according to dermatologists reporting to EPIDERM are rubber process operatives, electroplaters, galvanisers and colour coaters, hairdressers and barbers, and window dressers and floral arrangers. The occupations estimated to be at highest risk according to occupational physicians reporting to OPRA are electroplaters, galvanisers and colour coaters, chemical process plant operatives, glass products and ceramics makers, and chemists.
- The industries estimated to be at highest risk according to dermatologists reporting to EPIDERM are fishing, hairdressing, and mining and quarrying. The industries estimated to be at highest risk according to occupational physicians reporting to OPRA are manufacture of chemicals and chemical products, motor vehicles, non-metallic mineral products, and other transport equipment.
- The most common agents according to dermatologists reporting to EPIDERM are rubber chemicals and materials, wet work, and soaps and cleaners. The most common agents according to occupational physicians reporting to OPRA are rubber chemicals and materials, soaps and cleaners, other unspecified chemicals, and personal protective equipment.

Data from Health and Safety Commission (1998), Jones *et al.* (1998), Health and Safety Commission (2000)

Figure 2.4.3 Occupational dermatitis: Disablement benefit cases, by year



From 1996–1999 there were an estimated 9614 cases of work-related skin disease seen for the first time by dermatologists reporting to EPIDERM, and an estimated 8253 cases seen by occupational physicians reporting to OPRA. Assuming that there is little overlap between the schemes, these estimates can be added to produce an overall annual incidence of approximately 4500 cases per year. For EPIDERM and OPRA combined, the majority of estimated cases of skin disease were contact dermatitis (80%), with skin neoplasia, usually due to exposure to sunlight, (6.8%), other dermatoses (4.9%), contact urticaria (4.3%), and infectious skin disease (3.6%), the only other diagnoses contributing more than an estimated 1% of cases. Sixty per cent of the cases were estimated to be reported for males. An estimated 14% of cases occurred among men and women aged 16–24, with an estimated peak at 25–34 of 26%, declining to an estimated 4% of cases in men and women aged over 65. The age pattern is slightly different for males and females for contact dermatitis, with increasing incidence with age in men, but a higher incidence in younger age groups in women (Cherry *et al.*, 2000).

The overall rate of contact dermatitis reported to dermatologists over 1998–1999 was an estimated 8 cases per 100 000 workers per year, and for cases reported to occupational physicians was an estimated 6 cases per 100 000 workers per year. The occupations (SOC minor group) with the highest estimated rates of contact dermatitis reported to dermatologists were rubber process operatives (207 cases per 100 000 workers per year) electroplaters, galvanisers and colour coaters

(174 cases per 100 000), hairdressers and barbers (134 per 100 000), and window dressers and floral arrangers (126 per 100 000). The occupations with the highest rates of contact dermatitis reported to occupational physicians were electroplaters (221 cases per 100 000 per year), chemical process plant operatives (170 per 100 000), glass products and ceramics makers (155 per 100 000) and chemists (121 per 100 000). The rate of contact dermatitis has not been reported as high for electroplaters, galvanisers and colour coaters in previous analyses (Health and Safety Commission, 1998; Cherry *et al.*, 2000; Meyer *et al.*, 2000).

The most common agents, averaged over 1998 and 1999, which were associated with more than 10 cases in 1998 or 1999 for EPIDERM or OPRA are set out in Table 2.4.2. For dermatologists, the most prevalent substances were rubber chemicals and materials (average estimated 16%), wet work (13%), and soaps and cleaners (11%). For occupational physicians, the most prevalent substances were rubber chemicals and materials (average estimated 17%), soaps and cleaners (14%), other unspecified chemicals (13%), and personal protective equipment (12%).

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Table 2.4.2 Contact dermatitis analysed by causative substance. Average estimated cases reported by dermatologists and occupational physicians to EPIDERM and OPRA 1998–1999, Great Britain

Substance[a]	Dermatologists		Occupational physicians	
	Average estimated cases 1998–1999	%	Average estimated cases 1998–1999	%
Rubber chemicals and materials	**342**	**16**	**273**	**17**
Wet work	**276**	**13**	**151**	**9**
Soaps and cleaners	**241**	**11**	**231**	**14**
Nickel	**195**	**9**	37	2
Resins and acrylics	**156**	**7**	**128**	**8**
Preservatives	**131**	**6**	12	1
Chromium and chromates	**127**	**6**	6	0
Personal protective equipment (PPE)	**127**	**6**	**202**	**12**
Foods and flour	**127**	**6**	7	0
Petroleum and products	**127**	**6**	**104**	**6**
Aromatic amines (PPD)	**100**	**5**	18	1
Other biological substances	**95**	**4**	24	1
Solvents and alcohols	**89**	**4**	**40**	**2**
Fragrances and cosmetics	**86**	**4**	6	0
Hairdressing chemicals	**81**	**4**	6	0
Colophony and flux	**79**	**4**	19	1
Cutting oils and coolants	**77**	**4**	**110**	**7**
Aldehydes	**71**	**3**	18	1
Irritants (unspecified)	**69**	**3**	1	0
Cobalt and compounds	**66**	**3**	0	0
Friction	**65**	**3**	**60**	**4**
Glues and paints	**53**	**2**	48	3
Bleaches and sterilisers	**48**	**2**	42	3
Cements, plaster and masonry	**37**	**2**	26	2
Temperature and humidity	**18**	**1**	26	2
Metals and compounds	**17**	**1**	12	1
Other substances	**57**	**3**	**96**	**6**
Other unspecified chemicals	**183**	**9**	**208**	**13**
Total[b]	**2142**		**1619**	

[a] Substances with 10 or more actual cases reported each year to either EPIDERM or OPRA are shown. Where estimated cases are based on fewer than 10 actual cases, figures are shown in light type

[b] Total number of cases. Since some cases have more than one substance reported, percentages do not sum to 100

2.5 VARIABILITY AND SUSCEPTIBILITY TO OCCUPATIONAL AND ENVIRONMENTAL CONTAMINANTS*

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2.5.1 INTRODUCTION

When decisions or advice are given by expert advisory committees, agencies or government departments relating health effects to chemical exposures, such opinions can only be based on the available scientific and medical information, which may be very limited when it comes to human data. As an example, data on occupational exposure and ensuing health experience may be restricted to a small group of workers in one particular situation or a small number of volunteers who are often healthy young students. In neither case are the groups representative of

* David Gompertz is acknowledged for providing some of the information that went into this paper

the whole working population, nor of the rest of the population who may concomitantly be exposed due to work activities or unintended chemical releases.

In order to deal with the lack of human data and to take account of the fact that some individuals or groups will not be afforded protection by any recommendation for a standard or limit that is based on data from unrepresentative groups, uncertainty factors may be used to account for variability in human response. In addition or alternatively, qualitative caveats are often added as a supplement to standards, using the term 'susceptible individuals' or 'susceptible groups' to describe a theoretical population who may not receive the same level of protection, if any protection at all, at that standard. Often the term susceptible is never defined.

Standards set to protect the population from chemical exposures are set for a variety of risk management purposes, which include the following.

- Standard setting for human exposure. Such standards include occupational exposure limits in relation to the inhalation of substances in the working environment and acceptable daily intakes (ADIs) for chemical substances which may be introduced or found in the diet or drinking water.
- Special advice or precautions given to specified susceptible groups, such as limits on the intake of certain supplementary vitamins to pregnant women.
- Possible exclusion of susceptible individuals from certain occupational situations, such as exclusion of young people from occupational exposure to lead.
- The need for biological screening or bio-monitoring of susceptible individuals considered to be at greater risk from early reversible biological changes or early stages of ill-health.
- The need to give general population advice on specific chemical substances that may be found in the diet, water, certain foods or particular environmental situations. An example would be advice provided by the Department of Health (DH) on the maximum amount of red meat that should be consumed on a daily basis in order to limit the risk of certain types of cancer.

One further point of clarification relating to the terms variability and susceptibility is that both may be used in two broad contexts and thus cause some

confusion. The commonest use of both terms is related to biological variability or susceptibility, which can be the result of either inherent or acquired biological characteristics (e.g. genetics, age, gender, health status). The other use of the terms relates to exposure scenarios that will determine individual or group exposure and uptake. This use implies that an individual or specified group may receive a very different dose from the 'average' person for whom standards are often defined. This exposure variability is due to lifestyle and other factors that may be frequently encountered together among certain individuals and groups such as occupational, geographical location and dietary factors. There will of course be an interplay between the biological and exposure aspects.

There are further important factors to be taken into account in general approaches to dealing with variation and susceptibility in human response. One is the dose–response profile of exposure and effect for individual population members. Here, it is crucial for expert committees to know whether susceptibility in the human population is simply one end of a normal distribution curve or whether susceptible individuals are completely removed from the 'normal' population in their response.

In any population, including working populations, there will be a range of individual susceptibilities to occupational and environmental hazards. These may be genetic or may be associated with certain periods of growth and development, pre-existing disease and loss of function or excessive exposure by virtue of unusual lifestyles. These differences in susceptibility explain to a large extent why certain individuals in an exposed population suffer adverse consequences from an exposure and others do not (Rose, 1985). That there are major differences in any population is well established but their extent and underlying basis have not been fully explored, certainly not in relation to occupational or environmental hazards. Attempts have been made to review the effects of chemicals and pesticides for some age-related groups such as infants and children (IPCS, 1986; National Research Council, 1993). However, appreciation of the importance of vulnerable periods of development (Barker, 1994), factors affecting the development of allergic sensitisation (Cullinan & Newman Taylor, 1994) and newer hazards such as endocrine disrupters (IEH, 1995) shows that exposure at an early stage in development may have adverse effects at much later stages in life. Increasing knowledge of the genetic basis of toxic and allergic response to occupational and environmental hazards is allowing the identification of genetic subgroups at excessive risk.

2.5.2 FACTORS AFFECTING SUSCEPTIBILITY

GENETIC SUSCEPTIBILITY

The effects of many occupational and environmental carcinogens and toxins depend on a range of activating and detoxifying enzymes. The activity of these enzymes varies considerably between individuals, is related to the actual form of the enzyme present and is genetically determined. The proportion of individuals with these genetic variants (polymorphisms) may also differ widely in different populations (Parkinson, 1995). Epidemiological studies have shown that individual risk for a number of environmentally determined cancers (lung, bladder, colon) can be related to the genetically determined type and level of metabolising enzymes present (Hirvonen, 1995; Perera, 1996).

Genetic polymorphisms affecting toxic responses are not, however, restricted to the metabolism of organic toxicants. Polymorphism in the enzyme δ-minolaevulinic acid dehydrase (ALAD) is thought to be associated with lead susceptibility. Studies on the occurrence of two common genetic forms, $ALAD^1$ and $ALAD^2$, and blood lead levels have shown that individuals who are homozygous or heterozygous for $ALAD^2$ have significantly higher mean blood levels than those homozygous for $ALAD^1$. These observations support the hypothesis that there is a genetic basis for the observed inter-individual differences in susceptibility to lead toxicity (Todd *et al.*, 1996).

Although genetic polymorphisms in drug and toxic chemical metabolism have been identified and shown to be significant in establishing individual risk, there is less evidence implicating polymorphisms of immune system genes in susceptibility. However, relationships are being described between HLA genotypes and susceptibility to acid anhydride-induced asthma (Young *et al.,* 1995). Other studies of the relationships between genotype and allergic susceptibility are currently being performed.

THE EFFECTS OF GENDER

The effects of gender have to be considered together with both development and ageing. Sex differences in susceptibilities to toxic chemicals are widespread in experimental animals but have been documented to a lesser extent in humans (Calabrese, 1985). Often occupational investigations are performed or reported on males alone. The effects of endocrine disrupters on the developing reproductive system are clearly gender related. During adult life reproductive targets are different from those affected during early developmental stages and chemicals may affect a single sex; for example, different toxic chemicals are associated with male and female infertility. It has been suggested that the female breast may be a specific target for environmental carcinogens (Safe, 1997). The menopause, with changes in calcium homeostasis, is a vulnerable period for exposure of women to cadmium and other toxic metals (Chowdhury & Chandra, 1987).

SUSCEPTIBILITY OF THE FETUS, NEONATE AND INFANT

Owing to the fact that pregnant women and nursing mothers in the workplace may be exposed to a wide range of chemical substances, it is important to consider possible effects on the developing fetus, neonate and infant. The possibility of increased susceptibility to occupational or environmental chemical insult during very early stages of life has been addressed for specific groups of chemicals (e.g. pesticides, National Research Council, 1993). However, the current interest in the effects of impaired fetal and neonatal development on the causation of later adult disease (hypertension, coronary artery disease, chronic bronchitis) and the role of infections and allergic challenge during early vulnerable periods has widened the field of interest (Barker, 1994).

It is not the remit of this report, however, to discuss the effects of chemicals on the fetus, neonate or infant via the mother's exposure. The focus here is the possible added vulnerability of the pregnant or breast-feeding mother to chemical exposure.

SUSCEPTIBILITY DUE TO AGEING

Changes in physiological response to toxic hazards with age are difficult to separate from the effects of dietary change, co-existing disease and normal age-

related loss of functional reserve (Caird & Grimley Evans, 1996). Interestingly, the changing demography of the workforce (see Section 2.3) may lead to an increase in the working population of 'ageing workers' who are being exposed to occupational toxicants; thus this factor may take on an increasing importance.

THE EFFECTS OF PRE-EXISTING DISEASE OR MEDICATION

Pre-existing disease may make an individual more vulnerable to an occupational or environmental hazard by a number of mechanisms. Inflammatory changes in the respiratory mucosa of an asthmatic will sensitise that individual to acidic gases, cold air and exercise (Wardlaw, 1993). The effects of atopic eczema on the other hand may be to increase the dermal absorption of a pesticide, allowing systemic rather than just local toxic effects. Hepatic or renal disease reduces the ability to detoxify and excrete toxic materials. Thus any pre-existing disease may increase the sensitivity of a target tissue (toxicodynamic effects) or modify the ability to handle a toxic material (toxicokinetic effects). Similarly, concurrent medication can affect both sensitivity to a toxic material or the ability to deal with that material. The ability of various drugs to induce hepatic enzyme systems and thus modify the toxicity of subsequent xenobiotic materials is well established. Thus people on long-term anticonvulsant therapy might be considered at special risk from exposure to a range of organic toxicants.

BEHAVIOURAL AND LIFESTYLE EFFECTS

Varying behavioural patterns due to ethnicity, social class or occupation can give rise to exposure patterns that are sufficiently different to make the individuals involved more likely to exhibit the toxic effects associated with exposure to an occupational or environmental hazard.

Dietary habits, including the relative frequency of breast *versus* bottle feeding, vegetarianism and food preparation methods, affect exposure to food contaminants and also the ability to absorb them (IEH, 1997). The use of alcohol and tobacco has been shown to modify the uptake of and response to a range of drugs and environmental toxins.

Behavioural patterns such as the relative amount of time spent indoors, outdoors, at play or in cars are potential modifiers of exposure to such an extent that those with unusual patterns of exposure might be considered susceptible to toxic effects.

INTERACTIONS

A wide range of interactions between genetic factors, ethnicity, age and lifestyle are clearly possible. It was considered that Itai-itai disease following cadmium exposure in menopausal Japanese women was precipitated by their relatively poor state of calcium nutrition (Chowdhury & Chandra, 1987). Similarly, elderly people from ethnic minorities on restricted diets may be more vulnerable to toxic metal effects from traditional medicines. The effects of poverty as a mediator of occupational or environmental disease may act through a range of mechanisms, each increasing the susceptibility of the individual. Poor nutrition, early infections, use of tobacco and alcohol and exposure to increased toxic and immunological load may all interact to reduce the ability to detoxify chemicals and to increase organ and tissue sensitivity.

HYPERSENSITIVITY DUE TO UNKNOWN CAUSES

There is a group of individuals who report a range of disabling but non-specific symptoms following exposure at very low levels to multiple structurally unrelated chemicals. The term 'multiple chemical sensitivity syndrome' is one of a number of terms that have been given to this condition. Although it is clear that there are a number of people suffering from such a condition, its status as a toxicological syndrome is controversial and it has been viewed as having similarities to myalgic encephalomyelitis (ME) or chronic fatigue syndrome (Pennebaker, 1994; Fiedler & Kipen, 1997). A recent HSE-funded review summarising the situation has been published (Graveling *et al.*, 1999) and has drawn attention to possible psychological sensitivity in certain individuals as one explanation for the syndrome.

2.5.3 SOME EXAMPLES OF THE ROLE OF INDIVIDUAL SUSCEPTIBILITY IN THE DEVELOPMENT OF DISEASE

RESPIRATORY DISEASE

Genetic factors have been shown to be involved in a number of respiratory diseases associated with occupational or environmental exposures. α-Antitrypsin deficiency has been associated with emphysema and various HLA genotypes with acid anhydride-induced asthma. The importance of glutathione *S*-transferase phenotypes on neoplastic responses to asbestos and smoking has been reviewed (Hirvonen *et al.,* 1995).

Population studies of the determinants of asthma have indicated that the timing of childhood infections may play an important role in determining susceptibility to asthma from common environmental allergens (Cullinan & Newman Taylor, 1994). Other studies have attempted to identify those susceptible to episodes of outdoor air pollution.

CARDIOVASCULAR DISEASE

A large number of individual risk factors have been identified for cardiovascular disease. Susceptibility is affected by age, gender, nutrition, smoking, lifestyle and early developmental influences, that is, factors from all the groups listed in the Section 2.5.2 have been shown to be involved (Marmot & Mann, 1996).

CANCER

Cancer continues to be of major concern in occupational health thinking. Genetic susceptibility to a range of occupationally and environmentally induced cancers is

thus a subject of continuing interest and considerable research activity. It is well recognised that some polymorphisms in genes involved in the metabolism of various organic carcinogens give rise to very different levels of DNA adducts in individuals with similar exposure (Hirvonen *et al.,* 1995). Genetic variants of various DNA repair mechanisms are also well recognised (Perera, 1996). Both factors presumably affect variation in individual risk.

NEUROLOGICAL DISEASE

The early stages of development of the central nervous system are now well accepted to be particularly susceptible to toxic damage. Perinatal developmental neurotoxicology has been identified as a key area for study (IEH, 1996). There is also concern about the sensitivity of the nervous system to additional insult at the other extreme of life, when there is normally a progressive loss of function, and any additional progressive acceleration of the ageing process or extra loss, when functional reserve is at a minimum, may have serious consequences.

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2.6 VARIATION IN HEIGHT AND WEIGHT, BODY COMPOSITION AND PHYSICAL FITNESS OF THE UK WORKING POPULATION, ACCORDING TO AGE AND ETHNICITY

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2.6.1 INTRODUCTION

Anthropometric variation, particularly of height and weight, is relatively well documented in the UK population and there are plausible mechanisms linking these parameters to chemical exposure and adverse outcomes. Variation in body

composition has been rather neglected in this context but some precise and acceptable field methods have been developed and will be described, for example, Body Mass Index (BMI) and Bio-Impedance Analysis (BIA). Less information is available on the extent of, and mechanisms involved in, other types of biological variability, such as physical fitness and thermal tolerance, and of the modifying effects of, for example, the intensity of work and shift work on adverse health outcomes. How all these differ according to age and ethnicity has also to be considered.

2.6.2 VARIATION IN ANTHROPOMETRIC DATA

Anthropometric variation has three origins: inter-individual, intra-individual and secular. Inter-individual or phenotypic variation reflects the interaction of genotype and the environment. Of intra-individual variation, the effects of age on anthropometric parameters are rather obvious. Stature, weight and other bodily dimensions increase and become relatively stable by early adulthood, with the possible exception of weight and the fat component of the body. Before or soon after retirement age physical dimensions tend to decrease. Diurnal variation in stature due to lower hydration in the intervertebral discs is also well described. Its effects during measurement can be reduced by appropriate head 'lift' techniques.

The idea that people nowadays are taller and heavier than those of comparable age in previous decades and centuries is also familiar. Small suits of armour and low door lintels cause or confirm these suspicions. However, skeletal remains from Palaeolithic times suggest that the population then may have been taller and more robust than people are today. Except for a few select groups and countries, secular changes are still occurring, at an average rate of gain of 1 cm in adult stature and 2 kg in body weight per decade. Their origins are usually ascribed to improved nutrition and disease control.

2.6.3 MEASURES OF VARIATION

Variation can be measured in a variety of ways. The range is the simplest index but imparts information about only two measures in a sample or population. The standard deviation (SD) reflects the variability of the data and the accuracy and reliability of the measurement and is familiar to most biologists and human scientists. The coefficient of variation, (the SD divided by the mean), expresses the variation in terms of the average of the population. Centiles give more information about the distribution and frequency of values. They can be calculated from the raw data or from the mean and standard deviation and a set of constants (Pheasant, 1986; Karwowski & Marras, 1998). They are particularly useful in the present context as they can provide information about values near the ends of the range. Fifth and 95th percentiles are some of the commonest reported. Of course, just as there are no entirely 'normal' individuals, with all measurements at the 50th percentile, there are no short individuals of 5th percentile measurements or big people of all 95th percentile measurements. Z-scores ((x-mean)/SD) are also useful in that they are dimensionless and can be used to equate different parts of the distributions of variables in different units, for example, kilograms and metres.

2.6.4 THE EVIDENCE OF VARIATION

Anthropometric data on civilian populations of working age in the UK have been rather sparse. Some of the tables of data most well known to physicians and the public are the 'desirable weight' tables from the Metropolitan Life Insurance Company of the United States (Anon, 1983). These give weights associated with the lowest mortality according to age, gender, height and, supposedly, body build. However, there are considerable doubts over the applicability of the data to North American populations, let alone British populations, at the beginning of the 21st century. Large groups of male workers in light and heavy industry in the Midlands were measured by Khosla and Lowe (1968) and BP employees, mainly male office workers, by Montegriffo (1968) in the 1960s.

2.6.5 HEIGHTS AND WEIGHTS IN GREAT BRITAIN

The evidence of current levels of variation comes from annual or other large surveys of the population. The first nationally representative survey of the heights and weights of British adults was performed in 1980 (Knight, 1984). It was commissioned by the then Department of Health and Social Security as part of its programme of nutritional surveillance. Until then the best data of the national picture was the survey of Kemsley (1950) carried out in 1943 but based on a number of samples which could not readily be combined. Some of the data were collected in local chemist's shops using the chemist's equipment so there must be doubts about its reliability. Knight's sample was based on a multistage survey designed to cover all 16–64 year olds in a sample of 5000 households selected randomly from 100 local authorities stratified by type and by social class. Over 10 000 adults were weighed and measured in their own homes. The results are presented as mean, median and standard error of the mean for height, weight, weight for height, relative weight, and BMI (body weight (kg)/height (m^2)) for 5 year age and sex groups. The percentage distribution of each measurement is also presented. The effects of social class, region, parental and spousal measurements, family size and birth order, illness, drinking habits and recreational exercise were calculated.

2.6.6 HEALTH SURVEYS FOR ENGLAND

For the current population, the best height and weight data come from the Health Surveys for England (HS4E). The first HS4E was carried out in 1991 and the results published in 1993 (White *et al*., 1993). It was a part of an initiative to improve the nation's health, with an initial focus on cardiovascular health, the first of the five *Health of the Nation* priorities (DH, 1992), and on nutrition. The 1991 survey established the methodology and databases for subsequent annual surveys.

The 1991 survey was the first to measure all of the main risk factors for cardiovascular disease in a nationally representative sample of adults of all ages living in England. It began with about 3000 adults aged 16–64 years in 1991 but was enlarged in 1993 to include nearly 13 000 people. It provided data in the form of mean, median, standard error of the mean, and 5th, 10th, 90th and 95th percentiles on height, demi-span, weight, BMI and waist hip ratio (WHR, waist circumference/hip circumference). The associations with age, sex, social class, region and other socio-demographic characteristics, such as highest educational qualification obtained, marital status, housing tenure, household characteristics and ethnic group, were explored.

The reports of the HS4Es have continued in much the same form, although 1998 saw the publication of a report on the *Health of Young People* and by 1999, the latest report available, the annual investigation was titled *Cardiovascular Disease 1998* (Erens & Primatesta, 1999). The information on heights and weights presented in these reports is the most up-to-date currently available.

2.6.7 OTHER RECENT SOURCES OF HEIGHT AND WEIGHT DATA

- Dietary and Nutritional Survey of British Adults (Gregory *et al.*, 1990), surveys 1986–87, n = 2277
- Health and Lifestyle Study (Cox *et al.*, 1993), surveyed 1984/5 (HALS1) (n = 9000) and 1991/2 (HALS2) (n = 4400)
- Allied Dunbar National Fitness Survey (1992) surveyed 1990, 2400 men and women
- Birth cohort studies, all the births in 1 week in 1946 (Braddon *et al.*, 1986) and again in 1958 (Power *et al.*, 1997) followed up until the present
- British Standards Institution publications (http://www.bsi-global.com/index.html)
- People Size™ international database and software (Friendly Systems Ltd)*

* Friendly Systems Ltd *People Size™,* available [August 2001] at http://www.openerg.com/ or Open Ergonomics Ltd, Loughborough, Leicestershire, UK

2.6.8 THE EXTENT OF VARIATION

The various types of anthropometric measurement each show a characteristic variability in adults. Heights (stature, sitting height, etc) have a coefficient of variability (CV) of 3–5%, breadths and depths, 5–9% while total body weights have a CV of 10–20% (Kroemer *et al.*, 1990). Unusually large or small CVs suggest problems in sampling, measurement or data analysis.

2.6.9 HEIGHT, WEIGHT AND BMI: VARIATION ACCORDING TO AGE AND SEX

Results from the HS4E 1998 are shown in Tables 2.6.1 and 2.6.2. Heights of mature adults decrease with age, particularly after 65 years. This may be a true anatomical decrease as discs in the spinal column flatten or the spine and lower limbs become more curved. It may represent the effects of survivorship or of a secular trend in stature. Men are about 13 cm (5 in) taller than women on average.

Table 2.6.1 Distribution of height by age and sex in English adults in 1998*

		Height (cm)				
Age group (years)	**n**	**Mean**	**5th percentile**	**Median**	**95th percentile**	**95th–5th**
Men						
16–24	841	176.6	165.4	176.9	187.3	21.9
25–34	1298	176.6	165.5	176.3	188.0	22.5
35–44	1267	175.6	164.8	175.1	187.9	23.1
45–54	1236	174.8	163.9	174.7	186.3	22.4
55–64	935	173.1	161.4	173.1	184.3	22.9
Women						
16–24	980	163.4	152.6	163.5	174.2	21.6
25–34	1587	163.0	152.6	163.3	174.1	21.5
35–44	1540	162.5	152.5	162.3	173.2	20.7
45–54	1430	161.4	151.6	161.4	171.6	20.0
55–64	1083	160.2	152.2	160.1	170.4	18.2

* Data from Erens and Primatesta (1999)

Table 2.6.2 Distribution of weight by age and sex in English adults in 1998*

Age group (years)	n	Weight (kg) Mean	5th percentile	Median	95th percentile	95th–5th
Men						
16–24	827	73.3	55.9	71.8	97.6	41.7
25–34	1265	81.6	60.9	80.0	107.5	46.6
35–44	1235	82.3	62.7	80.7	107.2	44.5
45–54	1206	83.9	63.8	83.2	106.3	42.5
55–64	919	83.3	62.8	82.2	107.2	44.4
Women						
16–24	909	63.6	47.8	60.8	92.5	44.7
25–34	1441	67.8	49.8	64.8	95.7	45.9
35–44	1451	69.8	51.7	66.8	99.2	47.5
45–54	1385	70.4	51.3	68.3	96.5	45.2
55–64	1057	70.9	52.6	69.1	95.4	42.8

* Data from Erens and Primatesta (1999)

Mean weights increase with age but, contrary to most people's expectations, more before the age of 35 than afterwards. Again the effects of differential mortality may be having an effect. In the 1998 HS4E sample, men aged 25–34 years were 8.3 kg heavier than those aged 16–24 years but only 1.7 kg lighter than 55–64 year olds. In women the corresponding figures were 4.2 and 3.1 kg. The range of the 5th to 95th percentiles for height and weight are about 20 cm and 40 kg in 16–64 year old men and women. There were only small differences between the sexes and none with age.

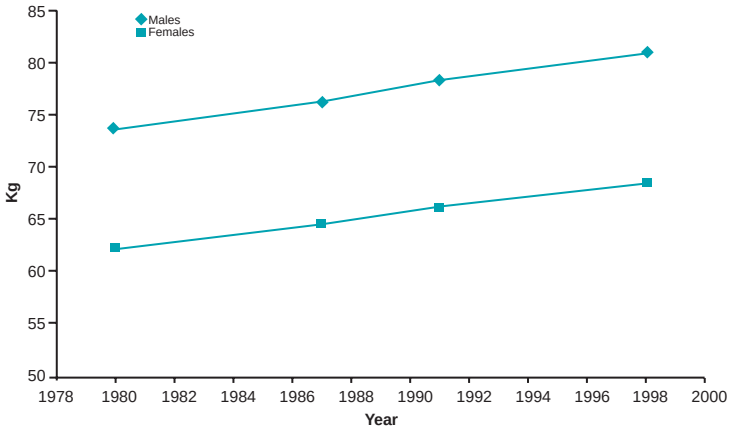
Body mass index increases with age in both men and women up to about 55–64 years. The mean BMIs of men are similar to those of women but the prevalence of obesity (BMI $\geq$ 30) is slightly greater in women. This does not mean that men and women are of equal fatness because the relationships between BMI and fatness are age and sex specific (Norgan 1994a) and may require standardising for body shape (Norgan & Jones, 1995).

Pheasant (1986) provides a succinct readable account of human sexual dimorphism. Men exceed women in all linear dimensions except hip breadth. Women also exceed men in measurements of subcutaneous adipose tissue. For height, the difference is about 13 cm or 7%, for weight, 12 kg or 16%.

The mean body weights of 16–64 year old men and women in England have risen over the 20 years since 1980, the period for which there are reliable representative

data (Knight, 1984; Gregory *et al*., 1990; White *et al*., 1993; Erens & Primatesta, 1999). These are shown in Figure 2.6.1. Such trends are a major public health concern, given the known sequelae of obesity. They have occurred at a time when levels of food intake appear to be decreasing, which suggests that the population is becoming remarkably sedentary. Activity deficiency may be the primary physiological deficiency in modern times.

Figure 2.6.1 The mean body weight of 16–64 year old men and women in England from 1980–1998



Data from Knight (1984), Gregory *et al*. (1990), White *et al*. (1993) and Erens and Primatesta (1999)

2.6.10 VARIATION ACCORDING TO SOCIOECONOMIC STATUS AND REGION

Variation according to socioeconomic status and region is not covered in the HS4E 1998 report but has been investigated in the other surveys listed above. In the UK, the relationship between BMI and social class varies with gender. In women, BMI has typically been reported to be higher in manual classes than in

non-manual classes. However, in men the relationship is less consistent between studies (Fehily, 1999). Regional variations in BMI are small.

2.6.11 BODY COMPOSITION

Our concepts of human body composition have been moulded by the techniques available for study *in vivo*. For many years, two-component models, such as the chemical model of fat and fat-free mass, or the anatomical model of adipose and lean tissue, held sway. More recently, combining methods of measurement has made possible, three- and four-component models of fat, water, protein and minerals. In the current context of adventitious chemicals in the body, the aqueous and fat components are probably the most relevant.

In the larger field of domiciliary studies of many hundreds or several thousand participants, the laboratory-based techniques of body volume, hydrogen isotope dilution, dual X-ray absorbtiometry and *in vivo* neutron activation analysis are not applicable. Instead, recourse is made to techniques that provide data that show strong relationships with that from laboratory-based methods. Two of the most commonly used indirect measures are the BMI and measurements of subcutaneous adipose tissue thickness, usually called skinfolds (Durnin & Womersley, 1974). Although not universally popular, such techniques are likely to be used for years to come, if only in that there are now baseline data that enable comparisons to be made. These measures have been joined by BIA as a popular field method. This operates on the principle that the impedance of the flow of a weak electric current through the body depends on the size of the aqueous phase. A number of assumptions are required to transform impedance and reactance to body composition, such as the body being a cylinder of constant radius and known length. This tends not to produce sensible results so that usually impedance itself and body composition are regressed to produce equations that enable body composition to be estimated from BIA, as in the case with skinfolds.

Comparative studies show that in expert hands skinfolds are probably the best of the three indirect methods. The advantage of BIA is that less training is required, undressing is minimal and precision of repeated measurements is best. This last point has led to BIA being used in preference to skinfolds in large surveys in the USA.

The three techniques all require age- and sex-specific estimation equations. This tends to be overlooked for BMI where the results are usually presented as kg/m^2. However, a given BMI is associated with a higher fat content (percentage of body weight) in a women than a man and in an older than a younger individual.

Fehily (1999) lists 32 papers and reports that provide data on adult body fatness in the UK over the last 20 years. However, only 20 of these are on groups of 500 or more people aged between 16 and 64 years of age. Most of the data are from BMI or skinfold thickness measurements. Missing from this list is the Allied Dunbar National Fitness Survey of 1990 (Allied Dunbar, 1992). Skinfold measurements were used to calculate percentage fat in 1169 men and 1206 women aged 16–64 years. As expected, mean percentage fat was higher in women than in men and increased with age.

Data from the Dietary and Nutritional Survey of British Adults (Gregory *et al.*, 1990) show the mid 90% range in body fatness to be 19% fat in 1143 men and 24% in 1134 women, a marked sex difference in comparison with the BMI. Reference values for fat-free and fat masses by BIA in 3393 healthy adults have been published recently (Pichard *et al.*, 2000).

2.6.12 FITNESS AND INTENSITY OF WORK

There is a shortage of good up-to-date information on national levels of energy expenditure, physical activity and fitness. Indeed the only data on fitness of a representative sample of the adult population come from the Allied Dunbar National Fitness Survey (Allied Dunbar, 1992).

The Allied Dunbar National Fitness Survey of 1990 was sponsored by Allied Dunbar plc, the Health Education Authority, the Sports Council and Department of Health (Allied Dunbar, 1992). Adults in 30 parliamentary constituencies throughout England were selected for interview in their homes and for physical appraisal in a mobile laboratory. Over 800 men and nearly 850 women aged 16–64 years completed the fitness tests. There are several dimensions to physical fitness and so handgrip strength, leg strength, leg power, aerobic capacity, lung function

and flexibility were assessed. The number of participants undergoing anthropometric and blood pressure measurements was 2376 and the number interviewed to provide information on health, lifestyle, social and personal attributes was 3393.

The results confirmed suspicions that the population of England was not very physically active. The differences in activity levels between social class groups was small and due in part to the different age compositions of the groups. A slightly higher proportion of those in the Office of Population, Censuses and Surveys (OPCS) social class categories I and II, the professional and intermediate non-manual group, engaged in vigorous activity than the other groups. It is suggested by Allied Dunbar (1992) that type of area or of housing might be more appropriate than targeting on social class alone.

Levels of cardiorespiratory (aerobic) fitness were extremely low — about one-third of middle-aged men and one-half of middle-aged women were "unfit" for continuous walking on the level at normal pace (about 3 mph) (Allied Dunbar, 1992).

2.6.13 ETHNIC VARIATION

Much of the original interest in anthropometry came from the fascination of anthropologists with human ethnic diversity. It is easy to find significant anthropometric differences between groups of different ethnic origin. In many cases, these differences are not great, and of little practical physiological significance, although they may be important in some design considerations (Kroemer *et al.*, 1990). There are some noticeable ethnic differences in body shape and proportions, from long-limbed black Africans to short-limbed Far Easterners (Pheasant, 1986; Norgan, 1994b). Humans seem to follow two rules concerning morphological variation: Bergman's rule that body size increases with decreasing mean annual temperature of the habitat; and Allen's rule that the relative size of the exposed portions of the body decreases with decreasing temperature. However, as we control the physical environment more and more and reduce temperature, dietary and disease variations much of the ethnic diversity of size and shape is disappearing too. Variations within groups are usually much more striking than variations between groups. Such between- and within-group

variation may have its origins less in genetic differences and more in socioeconomic status, employment and housing.

Frisancho (1990) has published separate tables for 1–74 year old US whites and blacks for height, weight, BMI and a variety of other anthropometric measurements for assessing growth and nutritional status. Good sources for recent reference data in various population and national groups can be found in Eveleth and Tanner (1990) and Karwowski and Marras (1998). It is important to remember that these are not standards or desirable levels but what has been found in populations in a variety of living conditions.

In the UK, death rates from coronary heart disease are higher in those from the Indian sub-continent than those of the white population, especially in women, but lower in those from the Caribbean. On the other hand, the latter group has the highest rates of stroke. The usual risk factors of weight and fatness do not fit neatly into the picture. Weights, BMI and body fatness have not been reported to be greater in Asians in the UK, except for a greater degree of central adiposity (Fehily, 1999). The mean BMI of African Caribbean men and women is slightly lower than that of European men and women, but the difference is not statistically significant (Fehily, 1999).

Heymsfield and colleagues in New York found that Chinese Asians had more fat for a given BMI than whites, in both men and women. Asians had more subcutaneous fat and more upper body fat than whites for a given level of fatness (Wang *et al*., 1994). In contrast, these authors confirmed that BMI as an indicator of body fatness is sex and age specific but it is ethnically independent in black and white adults (Gallagher *et al*., 1996).

2.6.14 THE CONSEQUENCES AND INTERPRETATIONS OF VARIATION

Size matters in many parts of the world for a variety of reasons. In developing countries, physical work capacity correlates positively with body size. Successful outcomes of pregnancy and lactation and resistance to infection may also be influenced by body size. However, the increasing size of the adult population in

Europe and North America and now in certain segments of the populations in developing and transitional countries reflects larger fat deposits more than bigger bodies of lean composition. Early sexual maturation accompanying accelerated growth is another phenomenon to which we do not seem well adapted, if only in the behavioural sense. However, delayed maturation and small adult size result from conditions of relative deprivation, which should not be tolerated in society. The cumulative and long-lasting effects of inequality are well documented and there is no reason why steps to reduce them cannot begin now (Wilkinson, 1996).

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2.7 SUSCEPTIBILITY TO INHALED CHEMICALS: VARIATION IN LUNG FUNCTION

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2.7.1 INTRODUCTION

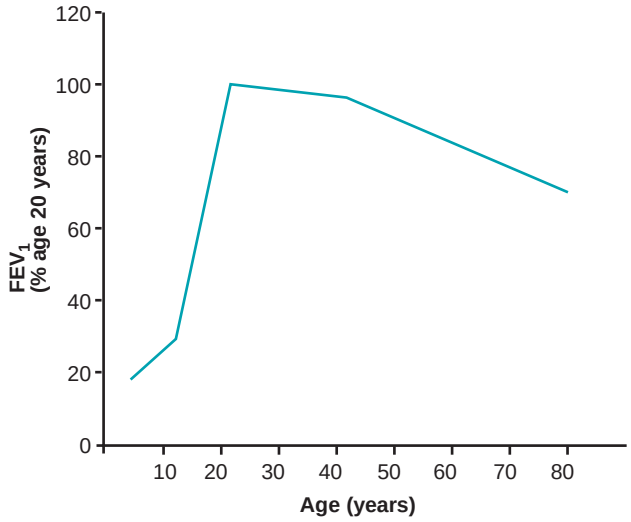
The function of the lungs is to secure the exchange of gas — oxygen (O_2) and carbon dioxide (CO_2) — between air and blood. To effect this exchange, air is conducted, via the conducting airways, to one side and blood, via the pulmonary circulation, to the other side of a thin membrane of large cross-sectional area, the alveoli, where O_2 passes from air to blood and CO_2 from blood to air down a pressure gradient. The function of the lungs would seem, therefore, to be most appropriately tested by measurement of the arterial partial pressure of O_2 and CO_2 (pO_2 and pCO_2) or by the alveolar–arterial pO_2 difference. Although such measurements are made, they are an impractical means of regular and repeated testing of lung function and do not measure directly the changes in the lungs most commonly responsible for respiratory impairment — narrowing of the bronchial airways. Two properties of airway function are commonly assessed: airway calibre

and airway responsiveness. Airway calibre can be measured in two ways: (1) the volume of air which can be expelled after a maximum inspiratory effort (vital capacity, VC) and the volume expelled in 1 s (forced expiratory volume, FEV_1); and (2) the flow rate during a forced vital capacity (FVC) manoeuvre, particularly the maximum flow rate (peak expiratory flow rate, PEF) but also the flow rate at lower lung volumes, for example 50% and 25% of vital capacity. In patients with airway narrowing the FEV_1, FEV_1/FVC ratio, PEF and flow rates at low lung volumes are reduced. Airway responsiveness is a measure of the ease with which a stimulus such as exercise, cold air, sulphur dioxide (SO_2), inhaled histamine or methacholine can provoke airway narrowing, most commonly measured as PC_{20}, the stimulus concentration that provokes a 20% fall in FEV_1. In patients with airway hyper-responsiveness, the strength of the stimulus required to provoke a 20% fall in FEV_1 is reduced (e.g. PC_{20} histamine is reduced from the normal >16 mg/ml).

2.7.2 DETERMINANTS OF LUNG FUNCTION

Airway branching is complete and the accompanying vessels present at birth; alveoli and pulmonary vessels continue to develop until age 8 years. The lungs increase in size during childhood and adolescence, achieving their maximum volume in the third decade. Vital capacity and FEV_1 are greater in boys and, as adults, men have larger lungs in relation to their body size. In adult life, from the mid 20s, after a plateau when maximum FEV_1 is attained, lung function deteriorates with increasing age, primarily due to loss of elastic recoil of the lungs (Figure 2.7.1). In healthy non-smoking men FEV_1 deteriorates by about 30 ml per year, possibly accelerating in old age. FEV_1 in adult life is therefore a function of the maximum FEV_1 attained, the duration of the plateau (or the time to the onset of decline) and the rate of FEV_1 decline. Cigarette smoking (passive *in utero* and infancy, active in adolescence) decreases the maximum FEV_1 attained, shortens the duration of the maximum FEV_1 plateau and accelerates the rate of FEV_1 decline, most markedly in the 'susceptible' smoker.

Figure 2.7.1 Changes in FEV_1 during childhood, adolescence and adulthood



The major determinants of FEV_1 and FVC in adults are age, gender, stature and ethnicity; FEV_1 and FVC diminish with age, are greater in men then women and increase with height although they are less for equal stature in persons of non-European descent (Fletcher & Peto, 1977). When these factors are taken into account FEV_1 is distributed normally around an average value with a standard deviation of about 0.5 l in adult men and 0.45 l in adult women, probably at all ages, and certainly during working life.

Measurement of airway responsiveness in community studies has shown that about 15% of the population have a measurable histamine or methacholine PC_{20}. The distribution of the frequency of airway hyper-responsiveness is U-shaped: it is more frequent in young adults, in whom it is associated with atopy, and in older adults in whom it is associated with cigarette smoking, probably because of associated reduction in FEV_1 (Britton *et al.,* 1994). The principal determinants of airway responsiveness in the general population are atopy and FEV_1.

The major influences on lung function in middle and later life are diet and infection in early life, and smoking in adult life. Tobacco smoking causes both an obstructive bronchiolitis and a destructive alveolar dissolution — emphysema — both of which accelerate FEV_1 loss by some three- to fourfold, causing disability

during working life and premature death. Low FEV_1 is a powerful predictor of premature death: in a 20 year follow-up study of nearly 3000 British men, Peto *et al.* (1983) found that, as compared with those whose $FEV_1/height^3$ (m^3) was greater than average, the risk of dying of chronic obstructive pulmonary disease (COPD) was increased 50-fold in those whose $FEV_1/height^3$ was 2 SD or more below the average value and 20-fold for those whose value was between 1 and 2 SD below average.

Several studies have suggested that early childhood events exert an important influence on adult lung function. In the 1980s, Barker and colleagues studied nearly 6000 English men born in Hertfordshire between 1911 and 1930 whose birth weights and childhood infections were recorded at the time by health visitors (Barker *et al.,* 1991). Fifty-five men had died of COPD; the standardised mortality ratio (SMR) at birth and at 1 year, progressively increased with lower weight. In a subgroup of 825 men born between 1920 and 1930 (aged at the time of the survey between 59 and 70 years), FEV_1 (adjusted for age and height) increased on average by 0.06 l for each 1 lb increase in birth weight, independent of socioeconomic status and tobacco smoking (Table 2.7.1). Bronchitis or pneumonia in infancy were associated with a lower FEV_1 (average reduction 0.17 l) independent of birth weight, socioeconomic status and tobacco smoking. Whooping cough in infancy was associated with a lower adult FEV_1, (average reduction of 0.22 l). However, no association was found between adult FEV_1 and lower respiratory tract infections at age between 1 and 5 years. The authors suggested that the association between adult FEV_1 and birth weight reflected impaired lung growth, particularly airway growth, during fetal life. Similarly, the impact of lower respiratory tract infections during the first, but not subsequent, years of life occurred during a critical period of infancy with persisting deleterious effects.

Table 2.7.1 Increasing FEV_1 in adult life with increasing birth weight in 825 Hertfordshire men born between 1920 and 1930

Birth weight (lb)	No. of men	FEV_1 (l/s)
≤5.5	33	2.28
6.5	103	2.41
7.5	258	2.44
8.5	242	2.52
9.5	132	2.55
>9.5	57	2.57
All	825	2.48*

* Standard deviation = 0.59

From Barker *et al.* (1991)

Improvement in maternal nutrition and reduction in the prevalence of lower respiratory tract infection in infancy since the first third of the 20th century should therefore be associated with progressive improvement in adult lung function. Some evidence for such an effect can be seen in the cohort effect of improving lung function. Whereas cross-sectional studies of FEV_1 suggest a reduction during working life of 30 ml per year, a cohort analysis over 5 years on the same population suggested a considerably smaller rate of fall, consistent with lung function (as assessed by FEV_1 in relation to adult height) increasing in successive generations (Figure 2.7.2). This difference can probably be explained by successive generations attaining a greater maximum FEV_1, each with comparable rates of decline. A cross-sectional view of FEV_1 therefore provides a snapshot of FEV_1 in a population which has declined from an increasing maximum in the younger age groups, thereby providing an artificially accelerated rate of decline; the true rate of decline is obtained by following FEV_1 longitudinally in a single cohort of similar age (Figure 2.7.3). Glindmeyer *et al.* (1982) have estimated that, at constant age and height, during the past 150 years VC has increased by 5 ml per year (i.e. 125 ml/25 years).

Figure 2.7.2 Difference between rates of decline in FEV_1 estimated in cross-sectional and cohort studies

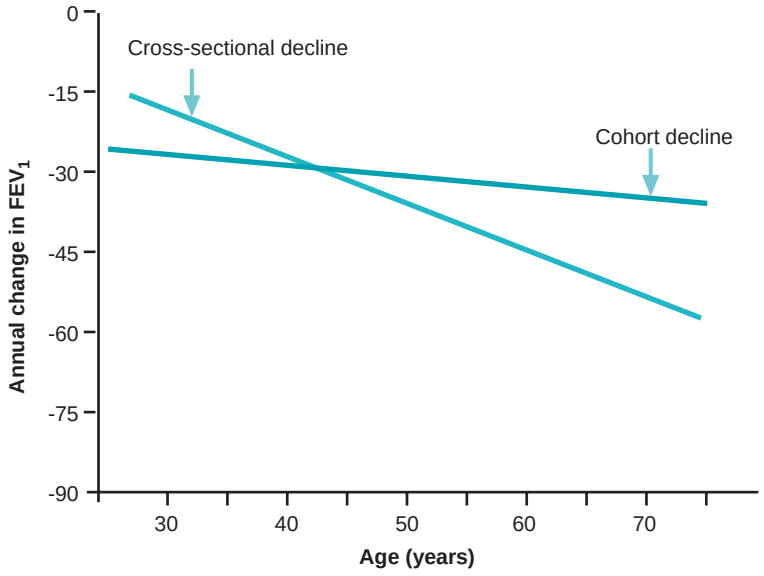
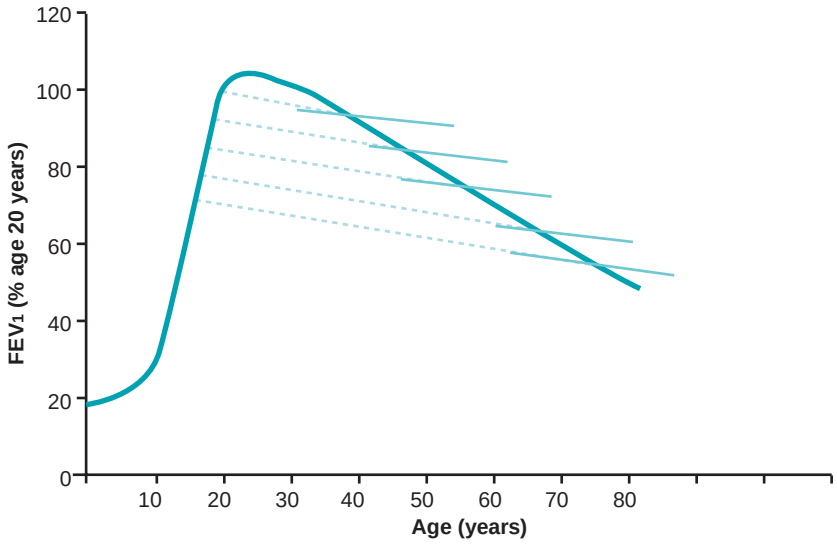


Figure 2.7.3 Explanation for apparent increase in rate of FEV_1 decline in cross-sectional compared with cohort studies: Although the rate of decline is similar, each successive generation attains a greater maximum FEV_1 from which to decline



From Glindmeyer *et al.* (1982)

2.7.3 AIRWAY HYPER-RESPONSIVENESS AND ASTHMA

The occurrence of airway hyper-responsiveness implies an increased responsiveness of the airways to non-specific provocative stimuli which include inhaled irritant chemicals such as SO_2. Individuals with hyper-responsive airways are therefore at increased risk of such chemicals provoking acute airway narrowing when inhaled in low concentration. Airway hyper-responsiveness is a cardinal feature of asthma, although measurable airway hyper-responsiveness can also be identified in individuals without asthma.

The prevalence, and probably incidence, of childhood asthma has increased in the past 20–30 years, probably by two- to threefold. This increase has been associated

with increasing material prosperity and attributed to many factors, most plausibly a reduced frequency of infection in childhood and possibly changes in diet during this period. The consequence is likely to be that an increasing proportion of those entering the workplace will have asthma and airway hyper-responsiveness, and a larger proportion of the workforce will comprise those whose childhood asthma has resolved, in about one-third of whom it will recur during working life. In addition the loss of ventilatory reserve with ageing, particularly in tobacco smokers, may increase the disabling effects of asthma in those who develop it either in the community or as a consequence of their work. This may in part explain the observation that the incidence of asthma reported to SWORD (Meredith, 1993) increases with increasing age: the true incidence may not vary with age, but the effect of airway narrowing and hyper-responsiveness, in those with already impaired ventilatory function, is likely to be greater and therefore more readily be brought to attention (Table 2.7.2).

Table 2.7.2 Incidence of occupational asthma reported to SWORD in relation to age and sex

Sex	Age group (yrs)	Observed cases	Observed rate (10^6/yr)	Standardised rate* (10^6/yr)
Male	16–29	167	17	11
	30–44	249	23	24
	>45	293	31	43
	All	709	24	
Female	16–29	89	11	9
	30–44	98	12	12
	>45	104	15	19
	All	286	13	

* Standardised for occupational disorder

From Meredith (1993)

Lung function, as estimated by FEV_1 in relation to stature, is probably increasing as a consequence of improvements in diet and hygiene in early life. The prevalence of tobacco smoking has fallen, particularly in males of socioeconomic groups 1 and 2, but is increasing in younger women. The prevalence of childhood asthma has increased probably by two- to threefold in the past two to three decades and, associated with this, the prevalence of airway hyper-responsiveness is likely to increase in adults of working age.

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2.8 XENOBIOTIC METABOLISM*

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2.8.1 INTRODUCTION

Risk assessment for threshold effects (non-cancer risk assessment) is usually dependent on the use of animal studies for hazard identification and definition of the critical effect. In most cases dose–response characterisation and risk assessment have to be made on the basis of the dose–response relationship available from animal studies. Uncertainties inherent in the establishment of safe intakes for the chronic exposure of the human population, based on oral toxicity data in animals, are allowed for by the use of a 100-fold safety or uncertainty factor. This factor comprises two 10-fold factors that allow for extrapolation from animals to humans, and from average human to sensitive human. These factors have been the subject of numerous reviews (Dourson & Stara, 1983; Calabrese, 1985; Hattis *et al.,* 1987; Renwick, 1991; Calabrese *et al*., 1992; Naumann & Weiderman, 1995; Renwick, 1995; Dourson *et al*., 1996; Renwick & Lazarus, 1998; Silverman *et al*., 1999; Vermeire *et al.,* 1999). An extra 10-fold factor was introduced under the Food Quality Protection Act (1996) in the USA to allow for the differences between infants and children compared with adults that could arise from different patterns of intake, and/or different susceptibility. This factor could be considered a database deficiency factor in those cases where the toxicity database did not cover the relevant life stages (Renwick *et al.,* 2000, 2001).

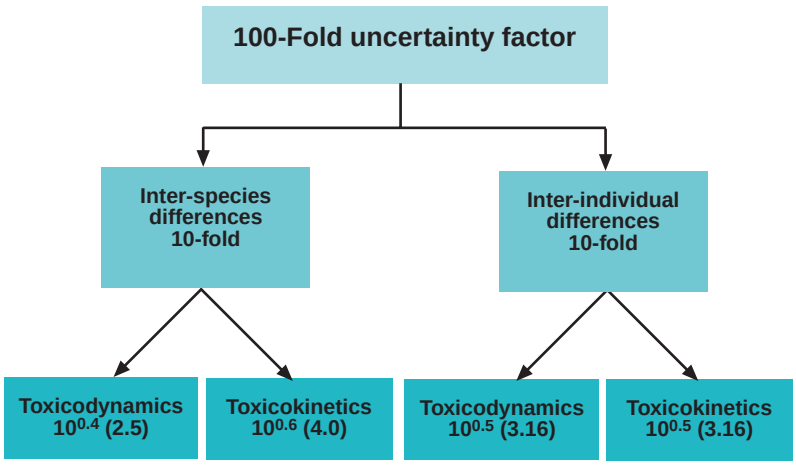
* Based on Renwick *et al.* (2001). The authors thank the Department of Health, and the Health and Safety Executive for jointly funding this work

The general default uncertainty factor of 10 for human variability applies to all metabolic pathways and routes of elimination, and also to all mechanisms of action. A single default value is difficult to justify scientifically given the known wide variability in some metabolic pathways in normal healthy adults, and the immaturity of some pathways of metabolism in neonates.

2.8.2 SUBDIVISION OF THE 10-FOLD FACTORS INTO TOXICOKINETIC AND TOXICODYNAMIC ASPECTS, AND THE USE OF CHEMICAL-SPECIFIC ADJUSTMENT FACTORS

Tenfold uncertainty factors have been used for approximately 40 years by a variety of national and international regulatory bodies to allow for inter-species differences and human variability. Each of these factors has to allow for two different areas of uncertainty, differences in toxicokinetics (the delivery of the active chemical species to the target for toxicity), and toxicodynamics (the response of the target organ in relation to the concentration delivered). Renwick (1993) proposed, on the basis of a limited database, that each 10-fold factor should be subdivided into separate default factors for toxicokinetics and toxicodynamics. Quantitative data for humans were essential to analyse the appropriate subdivision of each 10-fold factor, therefore the majority of examples that were analysed by Renwick (1993) related to the biodisposition and actions of therapeutic drugs. The subdivision was reviewed at a Task Group on Environmental Health Criteria for Guidance Values for Human Exposure Limits (IPCS, 1994), and factors of 3.16 ($10^{0.5}$) were proposed for human variability in toxicokinetics and toxicodynamics (Figure 2.8.1). This even subdivision has been supported by a recent analysis of human variability in pharmacokinetics and pharmacodynamics (Renwick & Lazarus, 1998).

Figure 2.8.1 Subdivision of the normal 100-fold uncertainty factor to allow for inter-species differences and human variability, and for toxicokinetic and toxicodynamic aspects



Based on IPCS (1994, 1999)

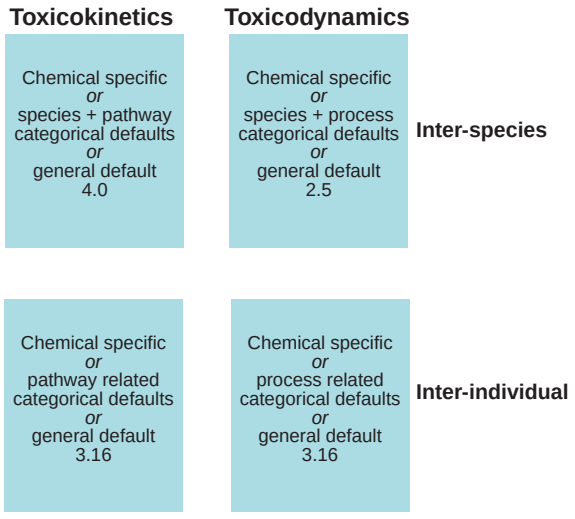
The main aim of the subdivision of the 10-fold factors is to allow relevant quantitative toxicokinetic or toxicodynamic data on the compound under evaluation to contribute directly to the uncertainty factor and hence to the calculation of a 'safe' intake. This would be achieved by replacing one of the default subfactors in Figure 2.8.1 by the quantitative chemical-specific data.

Only rarely are there sufficient compound-specific data to allow replacement of the default kinetic or dynamic factors for inter-species differences or human variability (Kroes *et al.*, 1993). Guidelines are currently under review within IPCS for criteria of suitability and adequacy of data that would be appropriate for the replacement of default factors. For inter-species differences, chemical-specific data on the toxicodynamics of the compound under evaluation could be produced from either *in vivo* kinetic–dynamic modelling in animals and a small group of humans (using appropriate, ethical and reversible biomarkers) or from *in vitro* data. However, *in vitro* data are not likely to be adequate for the assessment of the range of human variability in toxicodynamics, while any *in vivo* data would be used directly to establish the 'safe intake'. In contrast, toxicokinetic data on the compound under evaluation, based on studies at very low and 'safe' doses, may allow the kinetic default for human variability to be replaced.

2.8.3 INCORPORATING HUMAN VARIABILITY INTO RISK ASSESSMENT BY THE USE OF PATHWAY-RELATED CATEGORICAL DEFAULT FACTORS

In the absence of chemical-specific data there are a number of options by which refinements could be made to the current use of default factors. In many cases there will be information on the biological fate of the compound, for example renal excretion, or oxidative or conjugative metabolism, but appropriate chemical-specific, toxicokinetic data defining the internal dose. Renwick and Lazarus (1998) proposed an intermediate level of categorical default in which a range of default factors could be developed to be applied to different pathways of metabolism in the different test species compared with humans, and to human variability in the different pathways. In the absence of chemical-specific toxicokinetic or mechanistic data (which would allow the calculation of a chemical-specific adjustment factor), the known pathway of elimination or mode of action could be used to select an appropriate categorical default factor (Figure 2.8.2).

Figure 2.8.2
The development of categorical default factors as a 'half-way house' between chemical-specific adjustment factors and the general defaults given in Figure 2.8.1



A research project has been under way at Southampton University for the past two years generating a database from published studies in humans and animals in order to develop categorical defaults for the major pathways of xenobiotic elimination in humans and the main test species. There are currently over 700 references in the database on human kinetics and 500 related references on kinetics in test species. The methods of data identification, retrieval and analysis have been described in previous publications (Dorne *et al.*, 2001a,b; Walton *et al.*, 2001a–c).

2.8.4 PATHWAY-RELATED CATEGORICAL DEFAULTS FOR HUMAN VARIABILITY

The development of a pathway-related categorical default factor for human variability requires analysis of the population distribution of the relevant parameter and determination of the proportion of the population that the uncertainty factor is considered to cover. An analysis of human variability in kinetics or dynamics for a variety of compounds and effects (Renwick & Lazarus, 1998) indicated that an average of about 99% of the population would be covered by a default of 3.16 in a normal healthy population, assuming a log-normal distribution. The incidence of individuals who would not be covered by the composite 10-fold categorical default for human variability can be approximated as the product of the incidences not covered by the toxicokinetic and toxicodynamic defaults (Renwick, 1999).

The problems of establishing pathway-related categorical defaults for human variability are illustrated using the example of cytochrome P450 1A2 (CYP1A2), based on data from the publication of Dorne *et al.* (2001a). The proportion of the population covered by a chosen factor, or multiple of the mean, is dependent on a number of variables including:

- the nature of the population distribution, that is, normal, log-normal or skewed;
- the presence of genetic polymorphisms in the pathway of elimination that would influence the relevant kinetic parameters (such as clearance (CL) or area under plasma concentration–time curve (AUC)); and,

- the presence of susceptible subgroups that may be exposed to the chemical under assessment (such as neonates or the elderly — although these may be the subject of a separate risk assessment).

The *de novo* development of categorical defaults for particular pathways requires either:

- an initial a priori decision (by a risk manager) on the proportion of the general population that should be covered by the categorical default factors; or
- an analysis of all major pathways, to determine the overall average proportion of the population covered by the historical use of a default of 3.16, followed by definition of pathway-related factors to cover the same proportion.

Four substrates were identified for which CYP1A2 was the major route of elimination (caffeine, theophylline, paraxanthine and theobromine), and for which variability in AUC or CL, would represent variability in CYP1A2 activity. In addition, metabolic clearances via CYP1A2 have been published for warfarin, and for specific metabolic pathways for caffeine, theophylline, paraxanthine and theobromine. The percentage coefficient of variation for such metabolic clearance data ranged from 25–63%. Data on CL (expressed per kilogram body weight), CL (not adjusted for body weight), AUC and C_{max} (maximum plasma concentration) are available for a number of substrates and also for a number of potential 'at risk' subgroups. However, there was no consistent pattern of data availability for the different probe substrates.

The data from the various publications were pooled for each parameter using the weighted mean and weighted standard deviation values for the different numbers of subjects in each study contributing to the overall average (Dorne *et al.*, 2001a). The coefficient of variation for parameters related to chronic administration (CL or AUC) was approximately 40%, or about 38% for body weight-corrected estimates. There was a lower coefficient of variation (21%) for C_{max}, which is the parameter often related to toxicity following acute exposure.

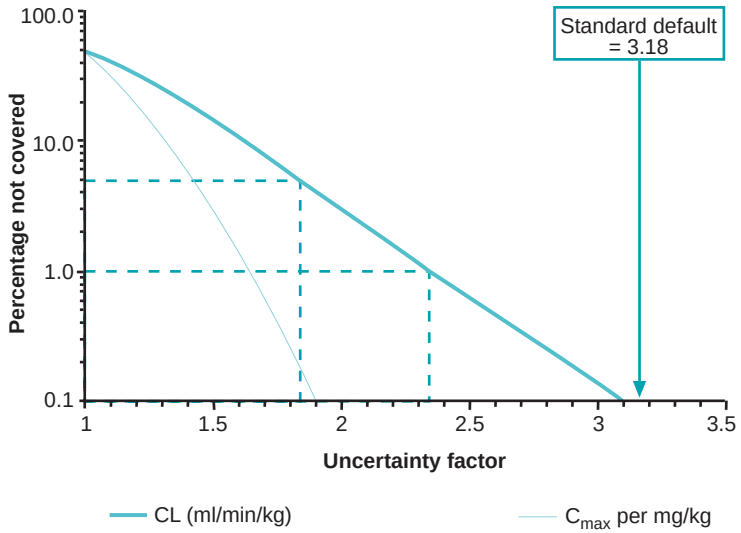
There is a relatively large amount of data on subgroups for two substrates of CYP1A2, caffeine and theophylline. Comparisons with healthy adults have to take into account differences in the mean parameter estimate and the coefficient of variation within the subgroup. The data in relation to age showed clearly that there would be much higher circulating steady-state concentrations in neonates

compared with healthy young adults (based on clearance data). The ratio of the values for neonates and adults differed between the two substrates and was approximately 3 for theophylline and 10 for caffeine, based on clearance estimates. CYP1A2 probably represents an extreme example of neonatal immaturity in xenobiotic metabolism compared with other isoenzymes or pathways of metabolism (Cresteil, 1998). The clearance in infants is similar to that in adults, although there may be greater variability, whereas clearance is generally higher in children compared with adults, resulting in a lower steady-state body burden in children than in healthy adults. In contrast, the elderly showed reduced clearance such that their internal dose would be higher than that in younger healthy adults. The limited available data on the maximum plasma concentrations after a single oral dose would suggest a lower peak exposure in neonates and the elderly compared with adults.

2.8.5 DEVELOPMENT OF CHEMICAL-SPECIFIC ADJUSTMENT FACTORS OR PATHWAY-RELATED DEFAULT FACTORS

The development of either a chemical-specific adjustment factor or a pathway-related default factor for human variability in healthy young adults will depend on the coefficient of variation, the population distribution model and the percentage of the population to be included within the default factor. Figure 2.8.3 indicates the factors that would be appropriate for a CYP1A2 pathway-related factor, based on clearance (38%) and C_{max} (21%), to include 95% and 99% of the population (assuming a log-normal distribution).

Figure 2.8.3 The development of a categorical default factor for human variability in CYP1A2 assuming a log-normal distribution



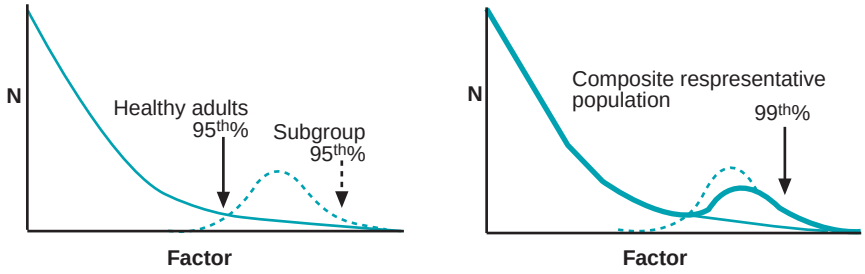
The coefficient of variation for clearance (CL) is 38% and for the peak concentration after a single dose (C_{max}) is 21%. The uncertainty factor selected is determined by the coefficient of variation and the percentage of the population to be covered by the factor (e.g. 95%, 99% or 99.9%). Adapted from Renwick *et al.* (2001)

There are two ways in which an adjustment factor for subgroups (such as neonates or those with specific genetic polymorphisms) could be calculated based on population distribution analysis (Figure 2.8.4). Silverman *et al.* (1999) proposed that the adjustment factor for sensitive subgroups should be based on a comparison of the 95th percentile for a subgroup with the 50th percentile of the general population. Such an analysis would not allow for differences in the incidence of the sensitive subpopulation. This approach would be logical for consideration of general subgroups such as neonates and the elderly or those with common polymorphisms, but it would not be appropriate for analysis of less common subgroups, such as those with rare genetic polymorphisms, which may be an inherent part of the general population and for which the individuals cannot be recognised (so that appropriate advice could be given by risk managers).

Figure 2.8.4 The development of a chemical-specific factor or a categorical default factor for human variability, allowing for a subgroup requiring a higher factor because of impaired elimination

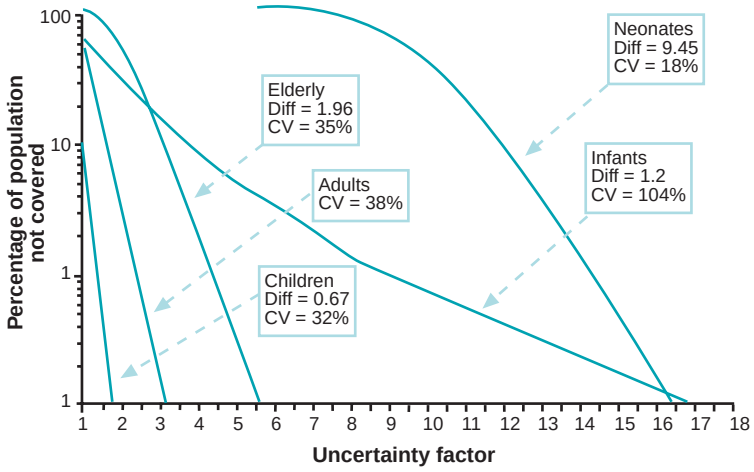
Should a constant proportion of the subgroup be covered (e.g. 90%, 95%, 99% etc)?
Should the incidence of the subgroup be taken into account?
Would it be logical to have a factor which covered 95% of a rare subgroup (e.g. 1:10 000)?
Would it be logical to have a factor which covered 99% of a whole population including subroups?

Alternative possibilities



An alternative general approach, which would be consistent across subgroups, would be to develop an uncertainty factor or adjustment factor which covered a constant proportion of the combined total population, that is, those that could not be given specific risk management advice. This analysis would have to take into account the difference in the population mean parameter estimates and the difference in the coefficient of variation (Renwick & Lazarus, 1998) and also the incidence of the subgroup(s). The data for caffeine in different age groups are shown in Figure 2.8.5, which illustrates the major difference between neonates and all other subgroups, and the difficulty of applying this approach. While a default factor that covered 95% or 99% of healthy adults would be reasonable for most of the other groups, the value would not be appropriate for neonates.

Figure 2.8.5 The development of categorical defaults for subgroups of different ages (based on data for caffeine) assuming a log-normal distribution



The clearances are for the oral route, except for the elderly where data are following intravenous dosage (the bioavailability of caffeine is 1). The uncertainty factor represents the difference between the mean clearance in adults and the population distribution of the clearance in the group. Adapted from Renwick et al. (2001)

Clearly neonates are not an 'at risk' group in relation to occupational exposures, where the main subgroups of concern will be those with impaired elimination due to hepatic or renal disease, or most especially, abnormal metabolism due to a genetic polymorphism. The problems of genetic polymorphisms are discussed in Section 2.9. The recognition and quantification of the influence of genetic polymorphisms of metabolism of a chemical on risk assessment will require the type of analysis given above for neonates.

A major issue with the use of chemical-specific adjustment factors, or the application of categorical default values, is determination of the active chemical entity, that is, the parent compound or the metabolite. In other words, is the pathway a detoxication pathway or part of an intoxication process? The analysis in Figure 2.8.5, which implies that a greatly increased factor would be needed for neonates, would be completely reversed if CYP1A2 were involved in the bioactivation of the compound and the generation of the toxic response, since neonates would be at reduced risk compared with adults.

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2.9 GENETIC VARIATION IN THE HUMAN POPULATION

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2.9.1 INTRODUCTION

Individuals differ from each other in many ways, and much of this variation has a genetic origin. When an allele at a given locus (gene) carries the same mutation in at least 1% of the population, the gene is said to exhibit a polymorphism. Polymorphisms do not normally cause any morbidity or other problems that would decrease reproductive efficiency. That is why a polymorphism can be maintained in a population at such a high frequency (>1–50%). Polymorphisms can be divided into two types. (1) Functional polymorphisms represent a change in the DNA sequence that results in altered expression or function of the protein, for example introduction of a protein termination codon. The presence of functional polymorphisms results in more than one phenotype for a genetic locus occurring in a species. (2) Nonfunctional polymorphisms are those in which there is a change in the DNA sequence that has no effect on the expression or activity of the protein, for example a change in the DNA sequence within an intron. Polymorphisms should be distinguished from inborn errors of metabolism. These usually cause serious ill-health (e.g. cystic fibrosis, phenylketonuria) and occur at extremely low frequencies in humans because sick people do not reproduce well and transfer the trait. Heterozygotes for a defect that is autosomal recessive transmit the trait to offspring.

2.9.2 GENETIC POLYMORPHISMS AND XENOBIOTIC METABOLISM

Polymorphisms are known to affect both the disposition of and response to xenobiotic chemicals, that is to affect both toxicokinetics and toxicodynamics. Such polymorphisms have been described as pharmacogenetic or toxicogenetic polymorphisms. The phenotype can often be determined by analysis of enzyme activity but is not usually recognised until a drug or other chemical associated with the deficiency is administered.

Many of the enzymes of xenobiotic metabolism exhibit functional polymorphisms. These include many of the cytochrome enzymes (e.g. CYP1B1, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5), flavin-containing monooxygenases (e.g. FMO3), alcohol and aldehyde dehydrogenases (ADH2, ADH3, ALDH2), monoamine oxidases (MAO A), microsomal epoxide hydrolase (EPHX1), esterases (e.g. PON1, PON2, BChE), *N*-acetyltransferases (NAT1, NAT2), glucuronyltransferases (e.g. UGT1A), sulphotransferases (e.g. SULT1A1), glutathione *S*-transferases (e.g. GSTM1, GSTP1, GSTT1) and many others. Subjects homozygous for the affected allele have reduced or no activity and are often referred to as poor (or slow) metabolisers (PM phenotype) whereas subjects carrying one or two copies of the unaffected allele ('wild type') are often referred to as extensive (or fast or rapid) metabolisers (EM phenotype). As in many other genetic disorders, many different alleles can give rise to the PM phenotype for a xenobiotic-metabolising enzyme, although usually only a relatively small number of alleles are responsible for the vast majority of PM subjects (e.g. approximately 40 alleles of CYP2D6 have been described that can give rise to the PM phenotype, but only four or five of these are needed to explain over 95% of PM subjects). There is usually a very good concordance between phenotype predicted from genotype and the actual phenotype determined experimentally.

While many alleles result in an absent or nonfunctional protein, some alleles can encode a product with reduced or altered activity. In the case of CYP2D6, there are at least six alleles that encode products with reduced catalytic activity towards typical substrates for the enzyme. However, this is not sufficient to result in the PM phenotype, even in subjects homozygous for such an allele. In other cases, as with ADH2 and ADH3, the mutation results in increased activity of the gene product. In other instances, for example the CYP2D6*2N allele, there is gene

amplification (N = 2–13), resulting in increased protein levels and a corresponding increase in enzyme activity (see Ingelman-Sundberg, 2001).

The consequence of this diversity of alleles at a single gene locus can mean that enzyme activity in the population does not exhibit a simple bimodal or trimodal distribution, representing those homozygous for the 'wild-type' allele and/or heterozygotes plus those homozygous for the mutant allele. Rather, there may be additional groups identifiable with intermediate activity (reduced function alleles) and ultra-rapid activity (increased activity alleles), as is the case for CYP2D6.

Polymorphisms of xenobiotic-metabolising enzymes can exhibit very marked inter-ethnic variation. For example 8% of Caucasians are PM for CYP2D6 while the frequency of this phenotype in Oriental populations is <1%. The opposite is true for CYP2C19, with only 3% PM subjects in Caucasian populations and 20% in Orientals. Similarly, the frequency of the fast acetylator phenotype of NAT2 can vary from 90% in Oriental populations to 10% in some African populations. Of interest is the fact that the alleles responsible for the PM phenotype often differ among different ethnic groups, and some alleles common in one population are absent in others. For example, the allele CYP2D6*10, encoding a form of P450 with reduced activity, occurs in only 3% of Caucasians, but in 51% of Orientals. This can complicate the use of genotype screens in populations of diverse ethnicity (see Kalow, 2001).

Toxicogenetics has focused largely on the enzymes of xenobiotic metabolism, with some emphasis from the late 1990s onwards on enzymes of DNA repair. However, in this context, it might be helpful to consider the processes involved in the toxicological response to a chemical. Chemicals enter the body and are then distributed to different cell types by passive diffusion, or facilitated or active transport. Since the mid-1990s, it has been recognised that there are many more carrier and transport proteins than originally believed. Once in the body, a chemical will be eliminated, either by excretion or by metabolism. Many of the systems involved can respond to the presence of a xenobiotic by upregulation, that is induction. Examples include many of the CYP P450 enzymes, GSTs and UGTs. Some chemicals, such as heavy metals, can be sequestered by specific proteins such as metallothionein, which aids in their elimination. In addition, such proteins are often inducible. Both parent compound and metabolites may be eliminated by passive diffusion, but there are a number of active transport systems, such as members of the multi-drug resistance glycoprotein family, which again are inducible.

Following distribution in the body, a chemical will interact with specific molecular targets. The response may be immediate repair, for example removal of DNA adducts or reduction of protein disulphides, inducible repair, for example involving O^6-alkyl guanine methyl transferase, or insult to the cell. Where cell damage is sustained this may result in the direct or indirect induction or suppression of specific pathways, such as heat shock proteins, redox active proteins, other stress proteins, cytokines, and many other proteins involved in homeostatic regulation. Hence, there is a multiplicity of factors involved in determining the outcome of a toxic response, both kinetic and dynamic. Any of these may exhibit genetic polymorphism, at least in theory. Such polymorphism could occur not only in the coding region, resulting in altered amounts or function of the gene product, but also in upstream regulatory regions or in the coding or regulatory regions of other genes involved in regulating their level of expression, for example induction receptors, stress sensors and other transcription factors.

2.9.3 SINGLE NUCLEOTIDE POLYMORPHISMS

Until the late 1990s, polymorphisms were believed to be comparatively rare. However, the Human Genome Project has established that all genes are polymorphic. The most recent estimate puts the number of genes in the human genome at 30–35 000, or around $1.9–2.2 \times 10^9$ bases. It has been estimated that the DNA of any two individuals differs by 1 nucleotide in approximately every 1000 bases. Such differences have been termed single nucleotide polymorphisms (SNPs), and they occur approximately every 1.9 kb throughout the genome, so that there are 200–300 SNPs per gene with a frequency of at least 1% within the population. This means that there are about 2.6×10^6 SNPs per genome/individual and over 1.1×10^7 SNPs within the population (see Kruglyak & Deborah, 2001).

Single nucleotide polymorphisms have been classified into three different types, based on their location within the genome. Coding region SNPs (cSNPs), as their name suggests, occur within the coding exons of genes. It is estimated that there may be 50–100 000 such SNPs. Perigenic SNPs (pSNPs) occur in the noncoding regions of genes, such as the introns, and the upstream and downstream

noncoding regions. There may be $2–5 \times 10^5$ pSNPs. The most common SNPs are the intergenic SNPs (iSNPs), which occur in the stretches of DNA between genes. It is estimated that there may be up to 2×10^6 such SNPs. The SNP Consortium, comprising groups from the public and private sectors, is currently creating an SNP map of the entire human genome.

While many SNPs are silent (have no functional consequence), they can be invaluable in establishing genetic linkage and hence in identifying genes which do show important functional differences. Of non-silent SNPs, that is those that result in a phenotype, many will be cSNPs, such that the structure of the gene product is altered. However, pSNPs may result in changes in the splicing, start or stop sites of transcription or translation, or may affect the interaction of regulatory proteins, either upstream or downstream of the coding region. The net effect is an alteration in the length of the expressed product, or a change in its level of expression. It was once thought that iSNPs would have no phenotype, but it is now apparent that gene regulation can occur at sites quite remote from the transcription start site, perhaps hundreds of kilobases upstream. Hence, even iSNPs cannot be ignored for their potential impact on gene expression.

Thus, SNPs can result in increased, decreased, absent or qualitatively altered activity due to altered stability or conformation of the gene product. In addition, mutations can occur in regulatory sequences, either increasing or decreasing protein expression. Finally, mutations may involve more than a single nucleotide, with deletion of up to the entire gene, or even gene duplication. Modern techniques enable the rapid detection of an ever increasing number of polymorphisms, and a major challenge will be to establish the functional significance of these.

2.9.4 TOXICOGENETICS AND SUSCEPTIBILITY TO CHEMICAL EXPOSURE

While many genes are now known to be polymorphic, the impact of this knowledge has largely been in toxicokinetics, rather than in toxicodynamics. In

part, this is because of the gap in understanding of the detailed molecular events involved in different toxicities, although this is rapidly changing. Indeed, by about 2002, rapid parallel advances in transcriptomics/proteomics and in identifying SNPs, allied with the availability of the sequence of the entire genome, will have enabled the identification of a very large number of candidate toxicodynamic polymorphisms.

The search for genetic factors that confer susceptibility to environmental exposures is placing unparalleled demands on techniques for identifying polymorphic alleles within individual subjects. Until the late 1990s, such alleles were identified one at a time by, for example, allele-specific polymerase chain reaction or by the presence or absence of specific restriction sites. However, the need is for techniques that will permit the simultaneous identification of hundreds or even thousands of alleles in large numbers of individuals. Groups such as Hirschhorn *et al.* (2000) and Fan *et al.* (2000) are developing approaches to eliminate this bottleneck.

The SNP Consortium will soon have identified SNPs at a density of >100 per gene. This, coupled with the availability of high throughput genotyping methods, is making mass genotyping a reality. However, it will be longer before the functional consequences of many of these SNPs are determined. Indeed, establishing whether just one SNP results in a phenotype currently can be very problematical. For example, there is still debate as to whether some of the polymorphisms of CYP1A1 and CYP2E1 are expressed at the functional level. In the USA, the National Institute of Environmental Health Sciences has established an extremely ambitious programme to identify all polymorphisms in the human genome with relevance to environmental effects, and to establish the functional consequences of these, through a combination of molecular and animal experiments. In the meantime, it is likely that many of the associations found between environmental exposures and genotype will be of unknown relevance for disease outcome, as they may either be chance findings due to the large number of comparisons that will be undertaken, or they will be due to linkage with another, unknown functional polymorphism, which represents the true risk factor. This can be exemplified by studies in the putative association between the CYP1A1 *Msp*I polymorphism and the risk of lung cancer from cigarette smoking. The increased risk in the m2 homozygote first reported in Japan is not observed consistently, either within Japan, or between different countries (see d'Errico *et al*. 1999; Houlston, 2000). Further, some groups have reported that the m2 allele is expressed at normal levels, with normal activity (e.g. Crofts *et al.* 1994).

As indicated above, most toxicogenetic research has focused on enzymes of xenobiotic metabolism. Despite the established role of these enzymes in the activation and detoxication of many environmental chemicals, in general, polymorphisms of these enzymes result in only a minor (less than twofold) increase in relative risk to the adverse effects of exposure. This has led to the suggestion that susceptibility is likely to be due to a combination of genotypes, which together increase relative risk by a substantial amount. The difficulties of analysing for such effects are severalfold. Group sizes will inevitably be low, reducing study power. The precise combination of genotypes leading to high risk is unlikely to be known *a priori*. Hence, it is likely that a large number of combinations will be analysed *a posteriori*, again reducing study power and increasing the likelihood of a chance finding.

In conclusion, it is now clear that genetic heterogeneity is the rule, not the exception and that all genes are polymorphic. However, by no mean all polymorphisms have a functional consequence, and establishing the functional consequence of a given mutation may not be trivial. Genetic variation could affect susceptibility in many ways. Both practitioners and regulators need to keep abreast of technological advances in this area and substantial consideration needs to be given to interpretation of data generated from such endeavours. All individuals (other than identical twins) will differ from each other at the majority of genetic loci. Many of these loci will eventually be shown to confer modest increases in relative risk to some exposures. The relevance of this for the exposed worker is not yet clear, but it is unlikely that it will be important for individual risk, for normal occupational chemical exposures.

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2.10 THE EFFECTS OF EXTRANEOUS FACTORS: PRE-EXISTING DISEASE, MEDICATION AND ALCOHOL

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2.10.1 INTRODUCTION

Pre-existing disease, prescribed medication and the consumption of alcohol (ethanol), either acutely or chronically, may affect an individual's response to occupational chemical exposures. In the case of pre-existing disease, this has led in some cases to pre-employment policies that restrict the employment of those individuals perceived to be at greater risk.

2.10.2 PRE-EXISTING DISEASE

As examples, the effects of pre-existing skin and respiratory diseases, glucose-6-phosphate dehydrogenase (G6PD) deficiency, inherited methaemoglobinaemia, ischaemic heart disease and glutathione deficiency on an individual's response to chemical exposures will be described briefly.

Atopic eczema (and to a lesser extent seborrhoeic eczema) is thought to render an individual more susceptible to contact irritants, but only if eczema was very severe in childhood and involved the hands (Rystedt, 1985). In addition, greater dermal absorption of chemicals occurs in workers with traumatised skin or extensive dermatitis. Those with moderate to severe asthma may be hyper-responsive to a wide range of chemicals that are encountered occupationally, for example isocyanates and chlorine.

Glucose-6-phosphate dehydrogenase is a key enzyme in redox metabolism. Deficiency of G6PD is an inherited condition that predisposes red cells to haemolysis and results in jaundice, haemoglobinuria, anaemia, malaise, abdominal pain and, rarely, renal failure. It affects an estimated 400 million predominantly male individuals worldwide. It has a high prevalence in those from Africa, Southern Europe, the Middle East and South-East Asia. As this condition is X-linked, men may be normal or G6PD deficient, whereas women may be normal, G6PD deficient (homozygous) or intermediate (heterozygous). In female heterozygotes each red cell is either normal or G6PD deficient. Red cells are vulnerable to oxidative damage both from oxygen radicals that are generated continually from within the red cells and from any oxidising agent that may be present in the plasma. These oxygen radicals are converted into hydrogen peroxide, which must be detoxified by glutathione peroxidase and catalase. Glucose-6-phosphate dehydrogenase is the first enzyme of the pentose phosphate pathway and catalyses the conversion of glucose-6-phosphate and NADP to 6-phosphogluconolactone and NADPH. Since NADPH is crucial for the operation of both glutathione peroxidase and catalase, the relative NADPH deficiency that ensues in those with G6PD deficiency renders red cells more susceptible to oxidative stress and hence to haemolysis. Older red cells, which are more deficient in G6PD, are destroyed preferentially. Individuals with G6PD deficiency are therefore at risk of developing haemolysis if they work in chemical plants manufacturing oxidizing substances such as naphthalene or trinitrotoluene

(Djerassi, 1998). For example, haemolysis can follow contact with naphthalene-impregnated clothing or inhalation of vapour. Workers with $G6PD^{A-}$, a variant encountered in Africans, need not be excluded routinely from work involving potential exposure to oxidising agents. This is because the concentration of such chemicals must be very high before haemolysis occurs (Amoruso *et al.*, 1986), as individuals with the $G6PD^{A-}$ variant are only moderately G6PD deficient (Goldstein *et al.*, 1985).

Methaemoglobinaemia is a condition characterised by increased quantities of haemoglobin in which the haem iron is oxidised to the ferric (Fe^{3+}) form. This results in impaired oxygen delivery to the tissues. Methaemoglobinaemia can result from an uncommon, autosomal recessive, inherited deficiency of red cell cytochrome b_5 reductase (red cell NADH-diaphorase; methaemoglobin reductase). Homozygotes have elevated methaemoglobin concentrations from birth, whereas heterozygotes are very susceptible to the oxidant action of drugs and chemicals. Heterozygotes should be advised against exposure to chemical agents, such as aniline, nitrobenzene, naphthalene and nitroglycerin, as even low concentrations of these chemicals are capable of inducing substantial methaemoglobinaemia in the presence of this pre-existing haemoglobinopathy.

The specific antidote for methaemoglobinaemia, methylene blue (methylthioninium chloride), utilises an NADPH-methaemoglobin reductase as the electron donor for reduction of ferric to ferrous haem. The NADPH-methaemoglobin reductase catalyses the reduction of methylene blue, to leukomethylene blue, which non-enzymatically transfers electrons to methaemoglobin, thereby restoring functional haemoglobin and methylene blue. Methylene blue should be used with caution in those with G6PD deficiency since the relative NADPH deficiency impairs methylene blue conversion to leukomethylene blue, so that not only can the antidote not function effectively, but non-reduced methylene blue may itself also precipitate haemolysis.

Workers with ischaemic heart disease are at greater risk of developing fatal arrhythmias and myocardial ischaemia if they are exposed, because of inadequate extraction equipment, to chlorinated hydrocarbons, such as trichloroethylene, tetrachloroethylene and 1,1,1-trichloroethane (Bailey *et al.*, 1997). Chlorinated hydrocarbons sensitise the myocardium to the action of endogenous catecholamines, thereby inducing ventricular tachycardia and fibrillation. Moreover, such arrhythmias are more likely to occur in those who have a history of ischaemic heart disease.

If non-smoking workers are exposed to the solvent methylene chloride, which is metabolised *in vivo* to carbon monoxide and carbon dioxide, they develop clinically significant carboxyhaemoglobin concentrations; the concentrations of carboxyhaemoglobin depend on the magnitude of exposure and the amount of activity undertaken during the period of exposure. It has been shown that non-smokers with coronary heart disease who have carboxyhaemoglobin concentrations of 2–6%, experience decreased exercise time to angina and an increased incidence of arrhythmias (Aronow *et al.*, 1972; Allred *et al.*, 1989; Kleinman *et al.*, 1989; Sheps *et al.*, 1990). It has also been shown that low concentrations of carbon monoxide produce significant effects on cardiac function during exercise in subjects with coronary heart disease (Allred *et al.*, 1991). However, occupational studies in workers chronically exposed to methylene chloride have not shown an increased morbidity and mortality (Hearne *et al.*, 1990; Lanes *et al.*, 1993; Tomenson *et al.*, 1997).

Carbon disulphide, used in the viscose rayon manufacturing industry, is a recognised causal factor of ischaemic heart disease (Sweetnam *et al.*, 1987; Swaen *et al.*, 1994; Peplonska *et al.*, 1996), although the mechanisms involved are unclear. It has been shown that occupational exposure to carbon disulphide increases total cholesterol concentrations and the risk of coronary heart disease (Kotseva & De Bacquer, 2000) and significantly increases the risk of pathological ECG abnormalities (Kuo *et al.*, 1997). As it is possible that carbon disulphide exposure only triggers ischaemic events in those with pre-existing ischaemic heart disease, workers so affected should avoid further exposure to carbon disulphide. This may be achieved by the introduction of improved hygiene or early retirement, as both would be expected to lead to a decrease in the incidence of carbon disulphide-induced ischaemic heart disease.

Glutathione, a tripeptide of glutamic acid, cysteine and glycine, is an important endogenous compound in Phase 2 metabolic reactions, which conjugate functional groups on molecules to form water-soluble, less toxic, polar derivatives that can be excreted renally. Excessive exposure to a variety of hydrocarbons, for example vinyl chloride and bromobenzene, leads to glutathione depletion in a dose-dependent manner and initiation of hepatic damage, much as in paracetamol poisoning. As pre-existing diseases such as anorexia nervosa or HIV infection (Staal *et al.*, 1992) can also lead to glutathione depletion, increased hepatic damage is likely to occur even after modest exposure to such chemicals in individuals with these diseases.

2.10.3 MEDICATION

Safe exposure levels at work are based on occupational exposure limits (OELs) that have been derived from animal experiments and experiments on humans who are not receiving medication. However, about 20% of a factory population take medication regularly (Rennie, 1985). In the UK it has been estimated that the mean number of prescriptions issued per head is 9.5 annually (Kirkness, 1997), although this number may be greater in the working population. Thus, potentially, many in the working population are at risk of accidents as their prescribed medication may contribute to adverse effects when they are also exposed to chemicals. In addition, chemical exposure may affect the efficacy of the prescribed medication.

Psychotropics are the drugs most commonly taken in a female working population (Lader, 1985), whereas male workers are prescribed cardiovascular drugs, such as beta-blockers, more commonly (Rennie, 1985). Psychotropic drugs can affect occupational performance adversely and beta-blockers may produce vasoconstriction and Raynaud's phenomenon, which may be exacerbated by the occupational environment.

The unwanted effects of medication may result from interactions with other drugs, with alcohol and with other chemical substances that may be encountered at work. For example, individuals who take medicines which depress the central nervous system and who work with solvents will be more impaired than those not receiving such medication; these effects will be compounded by concomitant alcohol intake. Some chemicals encountered in the workplace, for example polycyclic aromatic hydrocarbons and organochlorine pesticides, are enzyme inducers which can increase the rate of metabolism of some medicines being taken for pre-existing disease. In addition, patients prescribed enzyme-inducing drugs such as phenobarbital, carbamazepine or rifampicin, if exposed for example to bromobenzene, are more likely to develop hepatic necrosis. Workers prescribed cimetidine, erythromycin, or fluconazole, and who are exposed occupationally to chemicals, may develop prolonged features of intoxication as these drugs bind to microsomal cytochrome P450, thereby reducing the rate of metabolism of the occupational chemicals.

2.10.4 ALCOHOL ABUSE

About 12% of the working population in the UK have a drinking problem that may not only result in absenteeism, frequent accidents, changes in personality and erratic behaviour at work, but also increase the likelihood of central nervous system depression if, for example, workers are additionally exposed to solvents because of poor occupational hygiene. In addition, alcohol may also interfere with the metabolism of chemicals, thereby potentially either increasing or decreasing their toxicity as a consequence of enzyme inhibition or enzyme induction. The time elapsed after consumption of alcohol usually determines which of these two effects will dominate. During and shortly after drinking, when the blood ethanol concentration is high, it acts as an enzyme inhibitor. Later, when the blood ethanol concentration is lower, the inhibitory effect is less and the induction effect is more pronounced (Sato *et al.*, 1991). In addition, regular imbibing of alcohol may increase the metabolism of chemicals to which workers are exposed (Waldron *et al.*, 1983).

Ethanol-induced inhibition of solvent metabolism is well recognised and it has been shown in man that high ethanol concentrations can inhibit the metabolism of trichloroethylene (Müller *et al.*, 1975; Sato *et al.*, 1991), toluene (Waldron *et al.*, 1983; Døssing *et al.*, 1984; Wallén *et al.*, 1984; Bælum *et al.*, 1993; Imbriani & Ghittori, 1997), xylenes (Riihimäki *et al.*, 1982), styrene (Wilson *et al.*, 1983), and methyl ethyl ketone (Liira *et al.*, 1990). This occurs not only at the rate-limiting step catalysed by cytochrome P450 but also at subsequent steps, including alcohol and aldehyde dehydrogenase. For example, inhibition of trichloroethylene metabolism by ethanol results in accumulation of trichloroethylene and chloral hydrate (the latter is also employed as a sedative), which produces drowsiness and cardiac arrhythmias.

In an experimental study, 2 g ethanol administered daily to rats for three weeks increased the metabolism of 1,1,1-trichloroethane at exposure concentrations ≥273 mg/m^3 (≥50 ppm)* as shown by an increase in urine metabolites, although not a decrease in blood 1,1,1-trichloroethane concentrations (Kaneko *et al.*, 1994). In the same study, the metabolism of trichloroethylene was also found to be increased by ethanol as shown by a decrease in the blood trichloroethylene concentration as well as an increase in the urinary excretion of its metabolites. However, this effect was demonstrated only at high (>OEL) trichloroethylene

* Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming a temperature of 25 °C and a pressure of 101 kPa

concentrations (Kaneko *et al.*, 1994). Workers who abuse alcohol regularly are also likely to demonstrate a similar phenomenon, although the effect of induction is likely to be less marked at low trichloroethylene exposures where the rate of solvent metabolism is more affected by hepatic blood flow than the status of hepatic enzyme activity.

Tardif *et al.* (1994) demonstrated in volunteers that the administration of 137 g ethanol on two consecutive evenings before *m*-xylene exposure of 1737 mg/m^3 (400 ppm)* for 2 h resulted in decreased blood and alveolar *m*-xylene concentrations during and after exposure and increased urine excretion of *m*-methylhippuric acid at the end of exposure. At *m*-xylene concentrations of 4342 mg/m^3 (1000 ppm)*, no effect was observed.

In addition, consumption of alcohol after working with trichloroethylene may lead to transient reddening of the face and neck, known as 'degreaser's flush'. This condition, which often takes about 45–60 min to develop, is sometimes more severe than a simple flushing as it may be accompanied by chest discomfort and difficulty in breathing. The flush reaches maximum intensity 30 min after onset and fades within 60 min. It passes off after a few hours but will recur the next time alcohol is consumed. The mechanism is not completely understood but may involve competition between trichloroethylene and ethanol for aldehyde dehydrogenase (Müller *et al.*, 1975).

Alcohol is also known to potentiate carbon tetrachloride hepatotoxicity (Manno *et al.*, 1996). In experimental studies, the potentiation of hepatotoxicity depended more on the daily dose of alcohol administered than the duration of dosing (Shibayama, 1994). The precise mechanisms are yet to be elucidated.

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2.11 THE EFFECTS OF EXTRANEOUS FACTORS: PREGNANCY AND NURSING MOTHERS

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2.11.1 INTRODUCTION

Pregnancy involves two physiologies, that of the fetus and that of the mother. Although the purpose of this report is to address the potential added sensitivity of the pregnant and lactating woman to the effects of chemicals it is not always possible completely to separate the adverse effects on the mother from those on the fetus. Severe maternal toxicity is often related to secondary toxicity in the fetus.

Profound physiological changes occur in pregnancy, for example increases in cardiac output and in renal blood flow, leading to an increase in the rate of elimination of renally excreted drugs. Distribution volume may be altered owing to increases of up to 50% in plasma volume and 30% in cardiac output. There is an increase in renal and uterine blood flow to 600–700 l/min, and a mean increase of 8 l in body water (60% to placenta, fetus, amniotic fluid; 40% to maternal

tissues). This results in a decrease in the serum concentration of many drugs during pregnancy, especially those with a small volume of distribution.

Protein binding of drugs also falls, partly because of a decrease in serum albumin concentrations. Consequently, the unbound (free) fraction is increased, resulting in larger distribution volumes, which may also account for higher clearance rates of some drugs. These changes can significantly alter the natural course of diseases, and may alter the way the body handles drugs (increased or decreased plasma levels of some drugs), or both (Koren 1994; Becklake & Kauffmann 1999).

However, much less is known about the effects of pregnancy on the response of the mother to occupational chemical exposures. The pregnancy-related changes in fat content (Mattison, 1986) might increase the body burden of poorly metabolised lipophilic halogenated hydrocarbons. The consequences of such an increased body burden during lactation (Briggs *et al.,* 1994) and on the neonate are unknown. The pregnancy related changes in blood flow to the skin (de Sweit, 1980a) might be important for maternal absorption of environmental pollutants. Also, changes in pulmonary function occurring during pregnancy (Hytten & Leitch, 1971; de Sweit, 1980b) could mean that environmental or occupational standards for air quality should be altered.

The complex process of reproduction — maturation and transport of the germ cells, fertilisation, implantation, placentation and development of the conceptus and baby — occurs under precise hormonal regulation. Extraneous factors such as exposure to toxins, chemicals or environmental changes may disrupt these events, resulting in reproductive dysfunction or adverse pregnancy outcomes. Reproductive disorders include a large range of adverse outcomes that occur commonly. In the UK the incidence of spontaneous abortion is 10–20% in clinically recognised pregnancies. Among liveborn infants the malformation rate at birth is 2–3% and approximately 7% of newborns are of low birth weight. Developmental dysfunction is commonly diagnosed during the early years of life (Paul, 1997; McElhatton *et al*., 1999).

Although there is a widespread public perception that the majority of fetal malformations are caused by drugs or chemical exposures in pregnancy, this is not true. Drugs and chemicals together are thought to account for only about 4–6% of malformations. Most birth defects have no known cause.

Relatively little is known about the effects of workplace exposures specifically on female fertility, pregnancy and lactation. Most of the studies identified in literature searches concentrate on the effects of xenobiotic exposure on the fetus.

2.11.2 WORK-RELATED HAZARDS FOR PREGNANT WOMEN

It was noted in the early 1980s that an increasing number of women work in pregnancy and are stopping work later than they did (Chamberlain, 1993). Although paid employment has a generally beneficial effect on pregnancy outcome some specific factors such as strenuous work (Marbury, 1992; Fortier *et al.,* 1995), posture working on industrial machines (Gabbe & Turner, 1997), ionising radiation (Brent *et al.,* 1993), antineoplastic agents and ethylene glycol (Ahlborg & Hemminki, 1995), ethylene glycol ethers (NIOSH, 1991), polychlorinated biphenyls (Paul, 1997), methyl mercury (Lione, 1988), dry cleaning fluids and carbon monoxide (Koren *et al.,* 1991) may be hazardous for pregnant workers. Lead has also been reported to be associated with neurobehavioural abnormalities and growth deficits in the fetus (Paul, 1997). Theoretically pregnant women should no longer be occupationally exposed to high lead concentrations because of public health regulations; however, exposure to other sources such as in making stained glass, water contamination, paints, exhaust fumes and industrial waste cannot be ignored (Klein *et al.,* 1994).

Psychological stress is common in pregnancy and has been linked in some studies with frequent absence from work and possible premature deliveries (Ortayli *et al.,* 1996; Gabbe & Turner, 1997; Paul 1997). There is also an inherent concern for the well-being of the fetus. Exposure to xenobiotics at work, in the home or in the environment often adds to the stress. (Peel & Clarke, 1990; Hedegaard *et al.,* 1993; Lindbohm, 1999). Some studies have shown that fatigue and stress, particularly in the second trimester, whether related to work or home factors, contribute significantly to antenatal morbidity (Luke *et al.,* 1999).

The association between particular working conditions and adverse pregnancy outcome has recently been evaluated in a meta-analysis of published studies (Mozurkewich *et al.,* 2000). The meta-analysis was based on 160 988 women in

29 studies and factors such as physically demanding work, prolonged standing, long working hours, shift work and cumulative work fatigue score with premature births were evaluated. The association of physically demanding work with hypertension, or pre-eclampsia and small for dates (SFD) babies was also analysed. The results indicated that physically demanding work was significantly associated with premature births (OR 1.22; 95% CI 1.16–1.29), SFD (OR 1.37; 95% CI 1.30–1.44), and hypertension/pre-eclampsia (OR 1.60; 95% CI 1.30–1.96). Other occupational exposures significantly associated with premature birth included prolonged standing, shift and night work, and high cumulative work fatigue score. No significant association was found between long working hours and premature birth. The overall conclusion was that physically demanding work may significantly increase a woman's risk of adverse pregnancy outcome.

2.11.3 ESTIMATION OF EXPOSURE RISK

The presence of an agent in the workplace is not synonymous with exposure, since absorption into the body must occur for an adverse effect to be produced. Moreover, care must be taken to distinguish between exposure and poisoning. It is a commonly held view that exposure to chemicals may be dangerous, whereas exposure to medication is beneficial. Cognitive research has shown that the uncertainty about the risks of xenobiotic exposure to the pregnant and lactating woman makes it difficult for the mother to make complex health decisions (Polifka *et al.*, 1997).

2.11.4 HALOGENATED AROMATIC HYDROCARBONS

Halogenated aromatic hydrocarbons (e.g. tetrachlorodibenzodioxin, polychlorinated and polybrominated biphenyls) are a ubiquitous class of environmental pollutants that are of interest as reproductive toxicants because

they are highly lipid soluble and are cleared from the body very slowly. In addition the changing fat content of the body during pregnancy offers an additional cause for concern with these chemicals. During pregnancy the body fat content increases from 16.5 kg in the non-pregnant state to 20 kg by week 30 of gestation, falling to 19.8 kg at term (Hytten & Chamberlain, 1980). Following a single exposure to a lipid-soluble xenobiotic the compound is rapidly taken up into fat, but cleared very slowly. The decreasing fat content between weeks 30–40 results in a slightly higher xenobiotic concentration at term. Multiple exposures, either from intermittent or continuous exposures, result in a continuous rise in the concentration of these xenobiotics. Although the concentration of the xenobiotic appears lower during gestation, the effect of increasing fat content in pregnancy may actually increase the total body burden of lipid-soluble xenobiotics. Following delivery, the xenobiotic concentration in fat will increase with declining body fat content. This may pose an additional hazard to women who wish to breastfeed.

The results of a prospective controlled study of 125 pregnant women occupationally exposed to organic solvents in the first trimester between 1987 and 1996 showed significantly more malformations (13 *vs* 1; RR 13.0; 95% CI 1.8–99.5) in the infants in the exposed group compared with the controls who were exposed to a non-teratogenic agent (Khattak *et al.,* 1999). Similar results were reported from a cross-sectional study with retrospective pregnancy outcome data for women working in a control laboratory of a petrochemical plant (Vegieva *et al.,* 1998). There were also a number of children with health problems born to mothers who were exposed to the solvents for at least the first 2 months of pregnancy, usually in the higher exposure laboratories.

2.11.5 AIRBORNE POLLUTANTS

Other factors, such as increased blood flow to the upper extremities and increased pulmonary minute volume, may also act to enhance absorption of xenobiotics (Barlow & Sullivan, 1982; Mattison, 1986). During pregnancy pulmonary function is altered, predominantly by an increase in tidal volume from approximately 500–700 ml. Respiratory rate remains unchanged during pregnancy (1416 ml/min), therefore the minute ventilation is increased in parallel with the tidal volume, both increasing about 1.4-fold during pregnancy. The increase in minute ventilation during pregnancy means that the dose of airborne

pollutants delivered to the lung must also increase. For example, arsenic is transported across the placenta with fetal levels approximating maternal levels, often resulting in a higher incidence of spontaneous abortion or late fetal deaths. Infants of women working in, or residing near, a smelter were significantly lighter at birth. The threshold limit value for arsenic is 0.2 mg/m^3; during an 8 hour work exposure at that level, the non-pregnant woman would inhale 0.72 mg and the pregnant woman 1.01 mg, a significant increase.

Benzene has not only been associated with menstrual disorders but also with an increased risk of spontaneous abortions. It is thought that women are more susceptible to benzene toxicity because of their greater uptake and storage of this chemical in adipose tissue. The increase in both pulmonary uptake and body fat may place a special burden on pregnant workers. During an 8 hour work exposure at 31 mg/m^3, the non-pregnant woman will deliver 11.6 mg and the pregnant woman 16.2 mg of benzene to her lungs (Mattison, 1986). Similar results have been reported with ethylene oxide, used as a fumigant and for sterilising medical instruments. The amount delivered to the lungs during pregnancy is increased from 32.4 to 45.5 mg during an 8 hour work exposure. Ethylene oxide has also been associated with an increased risk of spontaneous abortions. These observations suggest that the increase in tidal volume during pregnancy may affect the quantity of airborne xenobiotics reaching the lung. Uptake into the lungs may also be altered in pregnancy because of the 1.5-fold increase in perfusion. These changes in pulmonary function and perfusion may exacerbate the adverse reproductive effects of other airborne pollutants such as vinyl chloride, which has been associated with human fetal malformations.

2.11.6 PHARMACOGENETICS

Pharmacogenetics is the study of inherited variability in response to drugs (Vogel, 1959). Variability in the disposition and effects of drugs also occurs during development (Manchester, 1986), but few data are available concerning chemical exposures (Grandjean, 1995).

2.11.7 GENDER DIFFERENCES IN AIRWAY BEHAVIOUR

During pregnancy asthma may remain unchanged, it may improve or it may get worse in roughly similar proportions (Stenius-Aaranalia *et al.,* 1996; Beecroft *et al.,* 1998). Exposure to solvents, dust particles, cleaning materials in the home, personal hygiene and beauty products, and environmental tobacco smoke (ETS) is thought to exacerbate asthma in some women (Becklake & Kauffmann, 1999). Gender differences in airway behaviour occur throughout the human life span. Airway dimensions relative to lung size, and differences in structure and functional relationships exist. For example, higher flow rates for a given lung volume are seen in girls and women than in boys and men (Becklake & Kauffmann, 1999). These differences are present *in utero* and persist into adulthood. Female airways are responsive to sex hormones and to their cyclical fluctuations. During pregnancy there is a change in lung and chest wall mechanics, progressive increase in transfer factor, which stabilises at about 26 weeks, and increased ventilation at rest and on effort attributed to increased progesterone levels (Dempsey *et al.,* 1996; Bates, 1998; Becklake & Kauffmann, 1999). However, peak flow rates remain stable throughout pregnancy (Brancazio *et al.,* 1997).

2.11.8 BREAST FEEDING

Data on excretion of drugs in breast milk are often poor or non-existent. Excretion of occupational chemicals in breast milk is also thought to occur but, in the majority of cases, data are lacking. Molecular size, pKa and the degree of protein binding influence the distribution of drugs into breast milk. As the pH of breast milk is more acidic than plasma, basic compounds may be trapped and reach higher concentrations in the milk. In general, drug binding to milk protein is less than to plasma proteins. Most drugs are excreted in small quantities in breast milk. However, this may not be true for highly lipid soluble compounds that are stored in the mother's body fat.

Most of the data available concern hydrocarbon solvents. The high lipid content of milk formed during lactation is an excellent route for excretion of these compounds (Jensen, 1983; Wolff, 1983). Chronic exposure may be particularly important for fat-soluble chemicals and some heavy metals that accumulate in the body. For example, the transmission of persistent fat-soluble organohalides to the suckling infant may be very high, exceeding the acceptable daily intakes (ADI) set by the World Health Organization (Rogan *et al.,* 1980). Accumulated compound in the maternal fat stores is translocated and excreted via the breast milk. There is one report of obstructive jaundice in a baby due to a chlorinated hydrocarbon in breast milk (Bagnell & Ellenberger, 1977). It has been estimated that a woman can actually get rid of half of her body burden of polychlorinated biphenyls by breast feeding (Grandjean, 1995).

In the Faroe Islands, hair mercury concentration was measured in 12 month old children when breast feeding had finished. The children who had been breast fed for the full 12 months had hair mercury levels 3 times greater than those of children who were not breast fed. There was no relationship with prenatal exposure to mercury.

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2.12 THE EFFECTS OF EXTRANEOUS FACTORS: NUTRITIONAL STATUS

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2.12.1 INTRODUCTION

Many toxic chemicals have to be metabolised in order to be eliminated from the body. While there appear to be metabolic pathways that are particularly efficient at dealing with exogenous chemicals, and some may have only that function, the majority of metabolic systems are probably directed to the processing of the single major complex chemical exposure to which every human is exposed on a daily basis, namely, the whole diet.

It has been known for almost 100 years that underfeeding has a profound protective effect on carcinogenesis. This protective effect is seen at all stages of carcinogenesis. The earliest observation (1914) was that underfeeding retarded the growth of transplanted tumours in mice. In the 1940s Albert Tanenbaum carried out a classic series of studies which clearly demonstrated that dietary restriction reduced the burden of spontaneous tumours, while at the same time increasing life span. More recently it has been shown that dietary restriction suppresses the action of several classes of carcinogens, including polyaromatic hydrocarbons,

alkylating agents and ionising radiation. There is also evidence that dietary restriction retards non-cancer ageing-associated pathologies such as nephropathy, cardiomyopathy, gastric ulcer and cataracts (Hursting & Kari, 1999). Perhaps because of the relative ease with which carcinogenesis can be manipulated in experimental models there is a greater body of literature on the phenomenon of the protective effect of dietary restriction. There are, however, relatively few data on humans, and a recent workshop on energy metabolism and carcinogenesis concluded that some caution had to be exercised in extrapolating the sometimes spectacular results in animals to the human situation (IEH, 2000).

2.12.2 EXPERIMENTAL EVIDENCE FOR NUTRITIONAL STATUS AS A MODULATOR OF TOXICITY BY CHEMICALS

As indicated above most of the available data relate to carcinogenesis (Table 2.12.1).

Table 2.12.1 The effect of dietary restriction on the incidence of experimentally induced tumours in rats, mice and hamsters

Tumour type/induction	Animal model	Route of exposure	DR[a]	Relative tumour incidence[b]
Chemically induced				
Skin	ABC mice	BP skin paint	33	2.3
	C47BL mice	BP injection	20	1.5
	DBA/2 mice	BP skin paint	40	3.0
	C57BL mice	BP skin paint	40	1.7
Intestinal	SD rats	MAM injection	25	4.5
Mammary	SD rats	DMBA injection	50	4.8
	F344 rats	DMBA injection	16	10.4
Liver	Swiss mice	DEN injection	30	>100.0
Cheek pouch	Hamster	DMBA injection	25	3.9
Physically induced				
Skin	C57 mice	UV light	30	12.4
Mammary	SD rats	X-ray	66	3.3
Leukaemia	SD rats	γ radiation	50	17.0

From Hursting and Kari (1999)
BP, benzo[a]pyrene; DEN, diethylnitrosoamine; DMBA, dimethyl benzanthracene; MAM, methylazoxymethanol
[a] Expressed as % of *ad libitum* diet consumed
[b] Ratio of tumour incidence in animals fed *ad libitum vs* diet restricted

There is evidence that dietary restriction affects all stages of the carcinogenic process. Dietary restriction can:

- modify carcinogen activation by inhibiting the enzymes responsible for that activation;
- enhance carcinogen detoxification by altering the levels of detoxifying enzymes;
- improve direct scavenging of DNA-reactive electrophiles; and
- enhance DNA repair processes.

The promotion/progression stages of carcinogenesis can be blocked by:

- scavenging reactive oxygen species, which in addition to acting at the initiation stage to damage DNA can also act at later stages to alter cell-signalling processes;
- altering the expression of oncogenes and tumour-suppressor genes;
- decreasing inflammation;
- suppressing proliferation;
- encouraging apoptosis; and
- enhancing anti-tumour surveillance.

Examples of modulation of all of these processes by dietary restriction are known (Hursting & Kari, 1999).

2.12.3 HUMAN EVIDENCE FOR NUTRITIONAL STATUS AS A MODULATOR OF TOXICITY BY CHEMICALS

It is now established that cancer is principally caused by environmental factors, of which the most important are tobacco, diet and factors related to diet, including body mass and physical activity, and exposures in the workplace and elsewhere (WCRF, 1997). In contrast to tobacco and occupational exposures, the aetiological agents for cancer in diet are largely unknown, which has made the study of the interaction between such agents and the whole diet somewhat difficult. The consideration of nutritional status as a contributor to disease risk has only relatively recently been incorporated into epidemiological studies. There is increasing evidence that the major burden of cancer risk comes not from exogenous chemical contaminants in diet but rather from endogenous processes that are intimately linked to normal physiological and metabolic processes. The inverse of the risk factors associated with diet is the fact that consumption of fruit and vegetables is consistently associated with lower risks of cancer. The mechanisms by which this protection is obtained are still not clear but extreme dietary patterns in humans offer some insight. Living food is an extreme uncooked vegan diet which results in dramatically higher levels of serum carotenoids (Hänninen *et al.,* 2000). Whether such a diet would afford protection against oxidation stress remains to be established. However, both experimental animal and human studies suggest that nutritional status would be likely to have an effect on toxicity resulting from exposure to extraneous chemical exposures in an occupational setting.

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2.13 THE EFFECTS OF CONSTITUTIONAL CONDITIONS: AGE, GENDER, OBESITY, THINNESS

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2.13.1 INTRODUCTION

The members of the workforce can generally be described as relatively healthy and active males and females aged 20–60 years from a range of ethnic groups. Within this group age is a major factor influencing health and response to chemicals (Cockcroft, 1997).

The working population is potentially exposed to a wide range of chemicals in the workplace, very often as mixtures. Chemical exposure may be short-term, for example high accidental exposure, or long-term, for example exposure to low levels of chemicals, potentially over a working lifetime of 40 years or more. Here the focus is on the influence of age on the response of the working population to

chemicals; other constitutional effects such as physical fitness and gender differences will be addressed in less detail.

Factors that influence response to chemical exposure include individual susceptibility and individual internal dose. Both of these parameters are potentially influenced by constitutional conditions, such as age and body weight. These factors must be considered in relation to other variables. It is difficult to separate the effects of age from those due to life style, diet or alcohol consumption. Large numbers of subjects are required for study and multiple regression analyses must be undertaken to identify the important variables. To eliminate the effects of constitutional conditions groups of workers matched for body weight and sex must be considered. To eliminate age effects it is necessary to study a narrow age band of less than 10 years (Consonni *et al.*, 1997).

2.13.2 FACTORS INFLUENCING THE INTERNAL DOSE OF CHEMICALS

Manifestation of toxic effects is related to the internal dose. Factors that influence the internal dose must be considered and these can include constitutional conditions (Williams, 1996). Internal dose, body burden or dose at target site are influenced by the physicochemical properties of the chemical, for example lipophilicity and its influence on uptake across membranes and distribution to tissues. Highly lipophilic molecules such as 1,1-di(4-chlorophenyl)-trichloroethane (DDT) and chlorinated pesticides are concentrated in the body fat, removing the chemical from the circulation but creating a significant and long-lasting body burden. Redistribution of a chemical in times of starvation or weight loss may be sufficient to elevate circulating blood levels and produce toxicity. The physicochemical properties of a chemical, such as volatility, can determine the route of exposure and hence the toxic effect by influencing the internal dose.

Internal dose can be monitored by measurement of haemoglobin adducts, DNA adducts, blood levels of the chemical or its active metabolite or urinary levels of water-soluble metabolite (often conjugates). Predictions of tissue pools and levels of chemical or metabolite at the target site can be made using physiologically-based pharmacokinetic models. Biological monitoring gives an indication of the

internal dose at the time of sampling but does not accurately indicate previous exposure unless the chemical has a long residence time in the body. Timing of spot samples is important.

Biological effect monitoring may extend biological monitoring; examples include determination of the effects of lead exposure on zinc protoporphyrin blood levels, assessment of genotoxicity by the COMET assay on peripheral blood lymphocytes and assay of urinary 8-hydroxy-deoxyguanosine levels or inhibition of red blood cell acetylcholinesterase to estimate organophosphate exposure.

AGE

Body burden of chemicals may increase with years of exposure and it may be difficult to distinguish age effects. For example, Sala *et al*. (1999) monitored the levels of organochlorine in serum from workers at a hexachlorobenzene factory and those living nearby. Workers had high levels of hexachlorobenzene, which were highest in the middle-aged men and declining in retired male workers. In the general population around the factory a range of organochlorines were found at levels related to eating contaminated fish and these also increased with age and body mass. Metals accumulate in bone, teeth and tissues such as erythrocytes. Long-term occupational exposure (analysed over 5 years) at greater than a mean blood lead of 31 µg/dl has been shown to be associated with a progressive sensory neuropathy (Chuang *et al*., 2000). The importance of the age of the workers was not considered.

The specific activity of xenobiotic metabolising enzymes in the liver has been shown to be independent of increasing age in humans for a number of enzymes, including cytochromes P450 (CYP), esterases, alcohol dehydrogenases and Phase 2 enzymes (Woodhouse & Wynne, 1992; Wynne *et al*., 1992). This differs from rodents in which sex differences in circulating hormone levels result in higher specific activities for cytochromes P450 in males compared with females. However, in humans the added effects of reduced liver size and liver blood flow with age contribute to reduced clearance of drugs from the liver (Rawlins *et al*., 1987). Changes are progressive, becoming evident by middle age (Wynne *et al*., 1989). O'Mahony *et al*. (1991) showed altered drug distribution and clearance in the elderly but no reduction in the activity of CYP1A1 in lymphocytes. Although the overall clearance of drugs and chemicals may be reduced with age owing to reduced liver size and blood flow, the relative balance between activation and

detoxification enzymes remains unchanged unless changes in physiology influence the cofactor balance, for example changes in the redox state of the cell. Similarly, polymorphisms of expression of xenobiotic enzymes should not change with age as they are related to genotype. However, Smith *et al*. (1991) showed age-related stereospecific changes in the increase in clearance of hexobarbitone isomers following rifampicin treatment in human volunteers.

There have been limited studies of variations in local metabolism with age that may influence environmental and occupational chemical exposure and toxic effects such as carcinogenesis. Development of chronic disorders of chemical exposure such as carcinogenesis have been shown to be related to chronic (cumulative) exposure and therefore duration of employment. This is difficult to separate from effects of increasing age in a workforce. Physiology changes with age and many chronic diseases develop and become more severe with increasing age.

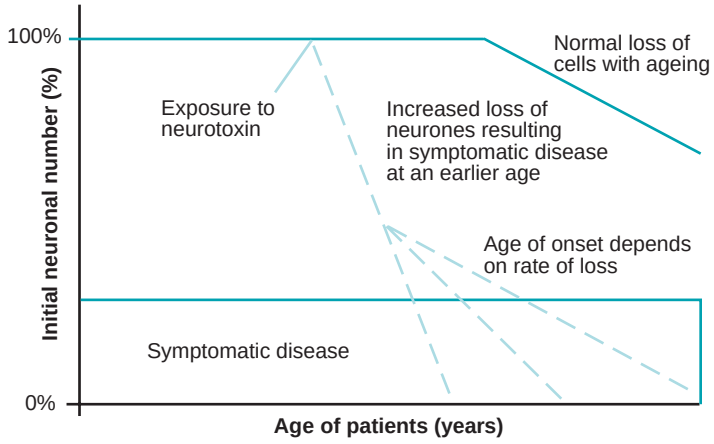
A particularly relevant age change is increased cellular oxidative stress leading to DNA damage. Many non-genotoxic carcinogens damage DNA by generating active free radicals which directly oxidise nitrogen bases. This can be monitored by the COMET assay in peripheral lymphocytes (for example, Collins *et al.* 1997a,b) or levels of the DNA repair product 8-hydroxy-deoxyguanosine in lymphocytes or urine (Loft *et al.,* 1992; Toraason, 1999). Contradictory reports suggest that age may (Fraga *et al.,* 1990; Loft *et al*., 1992) or may not (King *et al.,* 1997) affect the level of oxidative damage and repair. O'Mahony *et al.* (1994) have suggested that the elderly respond to environmental changes to a lesser degree than do the young. Liu *et al.* 1997 found an association between the incidence of 4977 bp deletions in mitochondrial DNA from the hair follicle with age and smoking index for current smokers although the age effects were most obvious in those over 70 years. Age-related damage to lymphocytes was detected by Bolognesi *et al*. (1997) who combined data from 12 Italian studies to obtain a sufficient population size. They measured micronuclei frequency, chromosomal aberrations and sister chromatid exchanges. The most dramatic increase found was in micronuclei frequency and of particular interest was a large increase in those aged 50–59 years, well within the age range of the working population. Increased oxidative damage was seen in patients with Alzheimer's disease (Mecocci *et al*., 1998).

It is also difficult to distinguish the influence of age from the cumulative effects of smoking or passive smoking. There is a relationship between age and number of years of smoking: for example, the incidence of colorectal cancer is related to

years of smoking and a greater number of the elderly develop colorectal cancer (Howard *et al*. 1998). Shinozaki *et al*. (1999) found a positive relationship between age and benzo[a]pyrene-diol-epoxide-deoxyribonucleic acid adduct levels in non-smokers (aged 22–66 years). In smokers, years smoked rather than age correlated with adduct levels.

There is a natural decrease in both neurone numbers and functional efficiency with age. The chronic effects of some neurotoxic chemicals and drugs may not become manifest unless function falls below a critical level with old age, for example Parkinsonism or the chronic effects of organophosphate exposure (Figure 2.13.1; Blain, 1996). These factors are generally not important in the majority of the workforce. However, retired workers (62–74 years) with previous long-term occupational exposure to solvents were studied. They had persistent central nervous system dysfunction years after the end of exposure (Daniell *et al*., 1999).

Figure 2.13.1 Increased rate of loss of neurones following exposure to a neurotoxin producing symptomatic neurological disease at an early age



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At the other extreme of age, children, although not generally members of the working population, must be considered as a special group and not just as small adults. Small babies are particularly susceptible to chemical exposure owing to their underdeveloped metabolising enzymes and immature skin permeability barrier.

GENDER

In general, only minor influences of gender on response to chemicals have been identified in humans. This situation differs significantly from that in animals where males often have a higher metabolic capacity than females and this may be associated with greater toxicity (Ballantyne *et al.*, 2000). For example, there is greater binding of aflatoxin B1 to DNA in liver hepatocytes from male rats than from female rats and male rats are more susceptible than female rats to hepatocarcinogenicity (Eaton & Gallagher, 1994). However, it has been observed in humans that males in Thailand have a higher incidence of hepatocellular carcinoma associated with exposure to aflatoxin B1 than females (Peers & Linsell, 1977). Several investigations have suggested that levels of CYP1A2 are lower in females than males and women taking oral contraceptives have lower CYP1A2 levels (Horn *et al.*, 1995; Rasmusen & Brosen, 1996). Activation of aflatoxin has been shown to correlate with CYP1A2 activity (Wilson *et al.*, 1997). There has been disagreement about the influence of gender on esterase activity. Williams *et al.* (1989) found no differences between males and females whereas Miners *et al.* (1986) found higher activity in males compared with females.

OBESITY AND THINNESS

There can be considerable differences between an obese individual and one with low body weight. The volume of distribution will differ and hence the circulating blood levels of a chemical and potential for toxic effects. These differences might have significance for susceptibility to toxicity in occupationally exposed individuals. There has been a general increase in body weight among people living in the developed world. Exposure limits that are currently set may be inappropriate for workers in the developing world where a poorer standard of living may result in a lower body weight and fat content.

Chlorinated pesticides and other highly lipophilic molecules may redistribute from fat stores in time of starvation, resulting in higher circulating levels and a potential for toxicity.

2.13.3 RECOMMENDATIONS

- Well-designed epidemiological studies of sufficient power are required to elucidate the effects of age on response to chemicals, particularly in the working population.
- Mechanistic studies must be designed to fill gaps in the understanding of the influence of constitutional factors on response to toxins.
- Early markers of effect could be studied in workers and related to age and years of cumulative exposure.
- There is a place for development of models to predict the interactions of age, gender and body composition with chemical exposure in relation to toxicity in the workforce.

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3 Discussion

3.1 CHANGING PATTERNS OF EMPLOYMENT AND VARIABILITY IN SUSCEPTIBILITY OF THE WORKFORCE TO EXPOSURE TO CHEMICALS

Work patterns in the UK have changed over the last 20 years and are continuing to do so (Sections 2.1 and 2.3). Employees change jobs more often than they used to and no longer think in terms of 'a job for life'. Such changing work patterns may result in exposure of workers to a variety of chemicals over varying periods of time rather than the same chemicals over a working life. In addition, over the last 20 years a steady decline has been noted in the number of heavy industries with large workforces. Currently 4.2 million (15% of the total workforce) are in manufacturing employment, representing a 16% reduction over the last 10 years (CBI, 2000). During this period, total employment has increased, primarily in the service industries and in small and medium-sized enterprises (Section 2.3). In the printing industry, for example, 170 000 people are employed in more than 12 000 companies, an average of 14 per company (Livesley & Rushton, 2000). Small businesses especially may have difficulties in carrying out the skilled assessments needed to introduce effective controls of exposure to chemicals. The very large number of micro enterprises (<10 employed) may well have particular problems. More needs to be known to understand how best to interact with such enterprises and their employees.

Variability in the response of humans to apparently similar or even identical occupational or environmental exposures can be due to individual differences in true personal exposure, toxicokinetics (the way the body handles a substance), toxicodynamics (the adverse effects the substance has on the body (including repair processes)) and the impact of existing injury, disease or loss of physiological or functional reserve. This report focuses only on biological variables and not on exposure variables as the latter would merit a workshop of their own. The word 'variability' as used in this report is often coupled with the term 'susceptibility' and the literature is liberally spread with a wide range of meanings, sometimes interchangeable, for both words. Here variability is used to describe the normal spread of values for a biological parameter such as lung function, or a biological response such as an irritation or odour threshold, in a given population. In general, many such biologically based variations conform to a defined distribution curve, although not necessarily a 'normal' one, as the nature of the curve may be influenced by a range of other biological variables such as age, gender, weight or genetic polymorphisms. In the case of the term 'susceptibility', definitions are more varied and it may be used to describe those individuals or groups within the general working population whose response to an exposure falls at the extreme lower end of the distribution curve, or those who fall outside the normal distribution and thus respond at much lower levels of exposure than the general population. Susceptibility may be related to an immunological or genetic difference that sets these individuals apart from the rest of the population. How such individuals are to be protected, whether falling at the lower end of a variability curve, or idiosyncratically susceptible, is a matter for risk management procedures and beyond the scope of this report. What is important, however, is to define clearly the population under consideration, the nature of the response and the factors that will impact upon that response. The key factors that may impact on an individual's response to chemical exposure are discussed in detail below.

3.2 DETERMINANTS OF VARIABILITY AND SUSCEPTIBILITY IN RESPONSE TO CHEMICAL EXPOSURE

Some variation in certain kinds of response to chemical insult, observed across the human population, cannot be attributed to any of the specific factors discussed in this report, for example an unknown proportion of observed variation may be attributable to variability in sensory perception and irritation. The threshold above which an exposure cannot be tolerated may vary between individuals, and from day to day for any one particular individual. This intolerance may be physiological or psychological, but in both cases could lead to symptoms and perceived ill-health.

3.2.1 METABOLIC VARIABILITY

Much is still unknown about the extent and significance of metabolic variation in the working population. Uncertainties inherent in the establishment of safe intakes for the long-term exposure of the human population are often allowed for by the use of a default safety or uncertainty factor of 100 (Section 2.8). This default uncertainty factor can be thought of as comprising two 10-fold factors (which are also subdivided) that allow for extrapolation from average animal to average human, and from average human to sensitive human. The data presented in Section 2.8 provide reassurance that the second of these two 10-fold uncertainty

factors is generally sufficient to allow for human variation. If current default approaches are to be refined, human data are essential. It is unlikely that the default approach will be replaced in the near future, as only rarely are there sufficient compound-specific data to allow the replacement of the default kinetic or dynamic factors for inter-species differences or human variability. Guidelines are currently under review within the World Health Organization's International Programme on Chemical Safety (IPCS) for criteria of suitability and adequacy of data that would be appropriate for the replacement of default factors (Section 2.8).

To avoid giving a false impression of the degree of metabolic variability, great care must be exercised when analysing and/or interpreting experimental and observational studies of toxicological response to chemicals because of difficulties in making accurate measurements. Ideally studies should be repeated on the same individuals, but this is not always possible for some endpoints. In addition, it may not always be possible to obtain information about an individual's previous chemical exposure(s) and the impact such exposure(s) might have on the variation in response to the chemical(s) in question.

A lot of work has been conducted to date on kinetic variability but there is scope to extend the work using physiologically-based pharmacokinetic modelling. At the University of Southampton a database is currently being generated from published studies in humans and animals in order to develop categorical defaults for the major pathways of xenobiotic elimination in humans and animals (Section 2.8). There are over 700 references in the database on human kinetics and 500 related references on kinetics in animals. Existing human data from databases such as this could be used to validate a model, which would then be used to predict the chemical kinetics for pathways without suitable probe substrates or *in vivo* data.

It is generally agreed that more is known about variability in toxicokinetics than in toxicodynamics; although information on toxicodynamics is difficult to obtain, it is still desirable. However, the overall response is easier to monitor and the best approach may be to look at kinetics and dynamics in tandem. Data on human response to pharmaceuticals have and are being generated by pharmaceutical companies in order to register their products. Most of these data relate to non-toxic, therapeutic doses of drugs; however, some data are generated for high doses, for example in the case of chemotherapeutic agents, and may be useful in studying human toxicodynamic variability. A project currently being conducted at the University of Southampton entitled 'A Study on Variation in Human

Toxicodynamics' (IGHRC, 2000) involves gathering and analysing the data available in the literature on human toxicodynamics. The extraction and comparison of information have been made difficult by the fact that different methods have been reported from different laboratories.

Further information on toxicokinetic and toxicodynamic variability in the workforce might be obtained by observational studies on individuals in working environments where their exposure and response can be measured accurately. This raises the question as to whether it is possible to be accurate enough to be confident that observed variation is due to biological variation, rather than analytical inaccuracies.

Another possible source of data is the National Poisons Information Service. Records of individuals admitted to hospital as a result of poisoning incidents contain information about their response to the intake of a particular chemical or chemicals; results of liver function tests are recorded, along with standard blood parameter measurements. These, together with blood levels of the chemical or biomarker(s), are recorded with time. Such information would allow comparison of the range of toxic responses and possibly provide an indication of the variability in response.

Owing to difficulties in extrapolating from animal to human data, animal experimentation is not an option to address the issue of human toxicodynamic variation. However it has been suggested that human tissue samples might be used to conduct *in vitro* tests.

It is important to realise that metabolism is a multistage process and that there can be deficiencies or variations at any number of points within the process, but this will not always produce changes in the overall metabolism of a compound. For a discussion of the implications of genetic polymorphisms, see Sections 2.9 and 3.2.12.

Biomonitoring of a population with the same chemical exposure and determination of the variability in response is feasible when biological surrogates can be identified and quantitatively related to exposure. This would enable measurement of subclinical early changes and avoid the need to wait for a clinical change to occur before a response could be observed. For example, measurement of FEV_1 (forced expiratory volume in 1 second) over time of a group of workers exposed to the same chemical could be used as a tool to examine the variability of lung function response to that particular chemical exposure.

3.2.2 BODY WEIGHT

Human body weight varies considerably across the working population (Section 2.6). Mean weight increases with age but, contrary to most people's expectations, more so before the age of 35 than afterwards. As expected, males are generally taller and heavier than females. As indicated in Section 2.6, the average weights of males and females are steadily increasing and the average male and female weighed approximately 81 and 68 kg, respectively, in 1998 in England.

Risk assessments are often conducted using average default body weights (e.g. 60 or 70 kg). The more recent data presented in Section 2.2 indicate that these average values need to be revised. Although further research is not required, existing data need to be compiled and examined to establish the current range of body weights in the UK. This information could then be used to inform risk assessors of the changes in average male and female body weights over the last 20 years, resulting in possible amendment of the standard body weight currently used in risk assessment. Using a range of body weights may be more appropriate for risk assessment. The compilation of these data would assist regulators in justifying the default body weight(s) chosen. The Environment Agency is currently conducting a review of body weights for inclusion in a re-evaluation of the default parameters used in the contaminated land exposure assessment (CLEA) model. Therefore it might be appropriate to await the outcome of this review before commencing any further data compilation.

3.2.3 LUNG FUNCTION, ASTHMA, ATOPY AND DERMATITIS

The lungs are important for exposure to chemicals in the workplace because they are the first point of contact for many chemicals. As explained in Section 2.7, the alveoli and pulmonary vessels of the lungs continue to develop until the age of eight. The lungs continue to increase in size during childhood and adolescence, achieving their maximum volume in the third decade. In adult life, from the mid-

20s, after a plateau when maximum FEV_1 is attained, lung function deteriorates with increasing age, primarily due to a decrease in the elastic recoil of the lungs.

The major influences on lung function in middle and later life are nutrition and infection in early life, and smoking in adult life. Lung function, as estimated by FEV_1 in relation to stature, is thought to be increasing as a consequence of improvements in diet and hygiene in early life and the falling prevalence of tobacco smoking, particularly in males of higher socioeconomic groups, although prevalence is increasing in younger women.

The prevalence and incidence of asthma has increased two- to threefold in the last 20 to 30 years. The consequence is likely to be that an increasing proportion of the workforce will have asthma and airways hyper-responsiveness. Of those whose childhood asthma has resolved, about one-third will be expected to have a reoccurrence during their working life. It was estimated (Section 2.7) that asthma and atopy levels in the workforce are probably in the region of 10–15% and 40–50%, respectively. However, actual levels in the working population are not known. In addition, it is not clear whether reporting and diagnosis have improved, thus increasing the apparent number of cases, or whether there is a real increase in prevalence. Clarification of all these points is required.

In particular, it is crucial that further research is carried out into the prevalence of asthma in the younger population. If this is indeed found to be increased and the increase is carried through into the working population then the proportion of workers who already have hypersensitive airways will be higher. Thus the problems of managing substances with even relatively simple effects such as respiratory irritation may become a problem as these could induce an asthmatic response in a previously hypersensitised individual.

In addition, asthmatics are not only hypersensitive to some inhaled chemicals, but also show unique characteristics following inhalation. For example the pattern of deposition of particles and aerosols differs between asthmatic and non-asthmatic individuals. In asthmatics deposition occurs in the tracheobronchial area of the lungs and clearance is more rapid than in non-asthmatics. Asthmatics also have a greater blood flow to the lungs than non-asthmatics. This could increase or decrease susceptibility to toxicity, depending on the chemical and whether the toxicity is local or systemic.

Many people have atopic eczema (Section 2.10) and this may render them more susceptible to contact irritants, particularly if the eczema was very severe in childhood and involved the hands.

Risk assessment of occupational chemicals does not currently include additional uncertainty factors specifically to protect individuals with existing asthma and atopy.

3.2.4 ALCOHOL

Alcohol may interfere with the metabolism of certain chemicals, thereby potentially either increasing or decreasing their toxicity as a consequence of enzyme inhibition or enzyme induction (Section 2.10). For example, inhibition of trichloroethylene metabolism by ethanol results in an accumulation of trichloroethylene and chloral hydrate, which produces drowsiness and cardiac arrhythmias. In addition, consumption of alcohol after working with trichloroethylene may lead to a transient reddening of the face and neck known as 'degreaser's flush'. Alcohol may remain in the blood for one or two days following a heavy drinking session and could potentially modify the effects of occupational exposure to certain chemicals. There may be sufficient data on workers in the UK exposed to organic solvents, in particular styrene, to enable this issue to be examined. Such a study would require a review of the available literature for information on blood levels of alcohol influencing the toxicological effects of occupational chemicals.

Long-term exposure to high levels of alcohol (as opposed to short-term low-level exposure) may result in induction or inhibition of enzymes. An appropriate biomarker for long-term alcohol intake levels does not currently exist and future research might investigate the development of such a marker. Although alcohol intake may eventually be considered in chemical risk assessments, it is only likely to have an influence in standard setting for a limited number of chemicals. Equally important is to educate workers where appropriate about the potential interactions between alcohol and the chemicals they are working with and the potential health and safety implications.

3.2.5 MEDICATION AND RECREATIONAL DRUGS

A wide range of medications and recreational drugs are used in the UK (Section 2.10). The number of workers taking medication or recreational drugs is not known; neither is the extent to which this may contribute towards their susceptibility to toxicity from occupational chemical exposure. For example, medications that may be of potential concern are antidepressants that may interact with solvents, and possibly psychotropic drugs. A survey of the working population to find out what medication and recreational drugs people are taking might be worthwhile.

Where there is knowledge of an interaction between prescribed drugs and chemical exposure in the workplace, ideally this should be highlighted to the employee where possible by the General Practitioner*. In such a situation, the employer could arrange alternative work until the employee has finished taking the medication or arrange a permanent alternative if the medication is to be taken indefinitely. However, in reality the General Practitioner will probably not know enough about an individual's chemical exposures in the workplace and it is highly probable that employees might see no reason to report their illness and prescribed medication. Such issues require consideration.

3.2.6 CIGARETTE SMOKING

One of the major influences on lung function in adult life is cigarette smoking. Tobacco smoking causes an obstructive bronchiolitis and a destructive alveolar dissolution, emphysema (Section 2.7). Both of these conditions can accelerate natural, age-related, FEV_1 loss by some three- to fourfold, causing disability during working life and premature death.

* All medications that cause drowsiness or have similar side effects come with warnings, and staff and employers are expected to adhere to the advice provided; that is, employees should not operate heavy machinery or handle dangerous substances.

Although a lot is known about smoking status and the extent of smoking in the UK workforce and its effects on health, it is not specifically taken into account in the risk assessment and risk management of occupational chemicals. However, where there is evidence of a synergistic risk in the causation of lung cancer, for example asbestos and smoking, this information is publicised.

3.2.7 PREGNANT WOMEN AND NURSING MOTHERS

Based on current trends it is estimated that there will be more women than men in the workforce in the UK by 2020 (Section 2.1, DTI, 2000)*. Therefore it is increasingly important that the physiology of the female worker, particularly the pregnant female worker, be taken into account when assessing potential exposure to chemicals.

There is a vast array of data available on the toxic effects of chemicals on the fetus and infant. This report, however, is devoted to examining the influence of pregnancy, a variable state, on the susceptibility of the mother to adverse effects from occupational chemical exposure. No known human examples were identified of occupational chemicals to which pregnant women are particularly susceptible.

Certain parameters, including lung tidal volume, renal blood flow, plasma volume and protein binding, undergo changes during pregnancy and could in theory affect the toxicity of chemicals whose kinetics depend on these parameters (Section 2.11). However, this area has not been explored. There is the general observation that pregnant experimental animals may be more sensitive to the toxic effect of chemicals than non-pregnant females of the same species/strain. Therefore it may be useful to review the experimental animal data for different classes of chemical to investigate whether the state of pregnancy induces increased susceptibility compared with the non-pregnant state. If such an effect were found, potential human susceptibility in pregnancy would need to be considered in occupational risk assessment.

* DTI (2000) *Foresight Ageing Population Panel Report*, London, UK, Department of Trade & Industry, available at http://www.foresight.gov.uk

There are data that show that mobilisation of certain chemicals, such as lead and polychlorinated biphenyls, occurs in breast-feeding mothers. Increased circulating levels of such chemicals could lead to adverse effects in the mother, although again there are no known data to support this.

3.2.8 CONCURRENT CHEMICAL EXPOSURES

Concurrent exposure to more than one chemical might increase or decrease the susceptibility of an individual to the toxicity of one of the chemicals; that is, one chemical exposure might influence the effect of another. This is an extremely complex area that is currently being investigated elsewhere*.

It is also possible that long-term exposure to an irritant, for example, may lead to acclimatisation, which may be manifested by decreased responses to this and other chemicals. However, it is not thought to be a major cause for concern.

3.2.9 AGE AND FUNCTIONAL RESERVE

The age of the UK work force is generally accepted to be 16 to 65 years of age. However, the age distribution within this range is now changing owing to many years of low birth rate and the ageing of those born during the post-war baby boom. People now tend to live longer, remain fitter and free from ill-health and want to do more in their senior years. The Foresight Ageing Population Panel has

* The Working Group for the Risk Assessment of Mixtures of Pesticides/Veterinary Medicines (WiGRAMP), a working group of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), is currently producing a report entitled *Risk Assessment of Mixtures of Pesticides and Similar Substances* to be published in 2002. The Interdepartmental Group on Health Risks from Chemicals (IGHRC), following the publication of the WiGRAMP report, may produce a position paper on the risk assessment of chemical mixtures.

stated that "Our older population is increasingly healthy, has much experience to offer and, on the whole, cannot be financially supported by the state as they live longer, leading us to the conclusion that it is in the UK's interest to make better use of its older workers by encouraging them to continue to work beyond the current state retirement age" (DTI, 2000)*. It was estimated that 12% of the workforce was over 60 years of age in 2000 and that percentage is predicted to increase to 16 and 19% in 2020 and 2030, respectively (Section 2.1; Figure 2.1.1). This may have consequences for susceptibility and variability of the workforce in response to chemical exposure as a result of loss of functional reserve.

There is an abundance of data on lung function; however, these data have not been evenly collected throughout the employment age range, particularly at the upper end. As previously discussed, lung function deteriorates with increasing age primarily due to a loss of elastic recoil of the lungs, and this age-related deterioration is greater in men than in women. Increasing the number of older workers is predicted to result in an increase in the number of workers with reduced lung capacity; this might be important, for example for dust-related effects such as clearance of particles. It is accepted that liver and kidney function do not deteriorate significantly with age. Where deterioration is observed it is generally due to a disease state that may remove the individual from the workplace. Therefore liver and kidney functional reserve are unlikely to alter an individual's susceptibility to chemical toxicity.

Some individuals may be at risk of post-retirement ill-health due to occupational chemical exposure. For example, individuals who work with neurotoxic chemicals, such as certain organic solvents, might only develop deficits in clinical neurological functional reserve after retirement. Section 2.13 refers to one study of retired workers (62–74 years of age) who had been exposed during their working life to solvents. These people had persistent central nervous system dysfunction years after the end of their exposure. The role of organic solvent exposure at work in the aetiology of this condition in retirement remains unclear. Similarly, subclinical effects in the liver and lung that develop during working life might lead to significant ill-health later in life. This possible post-retirement illness is not usually considered in risk assessments of occupational chemicals, as employees are generally not monitored once they leave their place of employment. In addition, there are very few data regarding changes in latency with increasing age.

* DTI (2000) *Foresight Ageing Population Panel Report*, London, UK, Department of Trade & Industry, available at http://www.foresight.gov.uk

It is difficult to separate age from other factors that might influence susceptibility to toxic chemicals, such as lifestyle, diet, weight, cigarette smoking, and alcoholic beverage consumption (Section 2.13). The occurrence of health effects that result from long-term chemical exposure, and therefore duration of employment, will be correlated with increasing age. These effects are difficult to differentiate from the effects of increasing age alone in the working population. Physiological changes occur with age, and many chronic diseases develop and become more severe, thus obscuring effects resulting from chemical exposure.

3.2.10 DIET

Nutritional status is likely to have an effect on the toxicity of extraneous chemical exposures in an occupational setting. However, there are many aspects of the diet that could influence susceptibility to chemical toxicity that currently cannot be disentangled from other factors. No clear subgroups were identified that stand out as being at increased risk of toxicity; the impact of any such subgroup is likely to be subsumed in the 10-fold default factor for interindividual differences. It is possible that particular dietary subgroups, such as vegans, may need special considerations in the risk assessment process, but currently there is no scientific justification for such action.

Nutritional status, in particular dietary and caloric restriction, can be manipulated in animal models with relative ease. The effects of this manipulation on the incidence of experimentally induced tumours in animals have been studied extensively (Section 2.12). It appears that dietary and caloric restriction does have a protective effect at all stages of the carcinogenic process. In particular, it is known that the capacity for DNA repair increases. However, caution is required in extrapolating these effects in animals to the human situation (IEH, 2000). Nutritional status as a contributor to disease risk has only recently been incorporated into epidemiological studies. Although diet is likely to have some influence, it is just too difficult to dissect this out from all the other potential factors.

3.2.11 GENDER, HEIGHT, BODY MASS INDEX AND FAT CONTENT

As described in Section 2.5, differences in susceptibility to toxic substances as a result of gender are widespread in experimental animals but have been documented to a far lesser extent in humans. Apart from special circumstances, such as consideration of chemicals known to be reproductive toxicants, there does not appear to be any evidence that gender *per se* influences susceptibility to chemical toxicity in humans.

There is wide variation across the working population in height, body mass index (BMI) and fat content (Section 2.6). However, the interindividual uncertainty factor of 10 is expected to include variability in the above factors. Further consideration of these factors in the risk assessment of occupational chemicals was considered unnecessary. No further research in these areas was identified as being required at present.

3.2.12 GENETIC POLYMORPHISM

The Human Genome Project has established that almost all genes are polymorphic (Section 2.9). It has been estimated that the DNA of any two individuals differs by one nucleotide in approximately every 1000 bases. There is currently an ongoing explosion of information about polymorphisms and the major challenge is to establish their functional significance. Caution needs to be exercised when reviewing and identifying polymorphisms in relation to response to xenobiotic exposure as not all have a functional consequence. As stated in Section 2.9, "Despite the established role of these enzymes in the activation and detoxication of many environmental chemicals, in general, polymorphisms of these enzymes result in only a minor (less than twofold) increase in relative risk to the adverse effects of exposure. This has led to the suggestion that susceptibility is likely to be due to a combination of genotypes, which together increase relative risk by a substantial amount". In addition, the presence of more than one

polymorphism in an individual may result in a cancelling effect as far as toxicity of a xenobiotic is concerned (see Sections 2.8 and 3.2.1).

It is recommended that investigators start with a phenotype and work backwards to the polymorphism that may be responsible: for example, the genotype of individuals who develop an illness/adverse effect could be examined in an attempt to identify the genetic basis for their susceptibility. At present not enough is known about the functional significance of genetic polymorphisms to explain variability and susceptibility to occupational chemicals. It was noted particularly that the distribution of genetic polymorphisms, irrespective of any consequences for metabolism of occupational toxicants, is likely to be no different in the working population than in the general population from which the workforce is drawn (Section 2.8).

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4 Recommendations

A key point to emerge from the workshop was the recognition that variability and susceptibility in the working population are unlikely to be significantly different from that in the general adult population. Taking into account the reviews presented in Section 2 and the general discussion summarised in Section 3, a number of recommendations are made for research to increase knowledge about susceptibility and variability within the working population and improve approaches to the regulation of occupational chemicals. No attempt has been made to set priorities for the proposed actions, and recommendations are listed under the topic headings used in Section 3.

METABOLIC PATHWAY VARIABILITY

- Human data from existing databases could be used to validate a physiologically-based pharmacokinetic model, which could be used to predict the chemical kinetics for pathways without suitable probe substrates or *in vivo* data.
- Observational studies on variability in response to routine exposure to certain chemicals in the workplace should be conducted by recruiting individuals working in environments where their exposure and response can be readily monitored.
- Data (for example, blood parameter measurements, liver function tests, blood levels of chemical over time) from the National Poisons Information Service should be examined to compare the range of toxic responses to a particular chemical for a range of individuals, to obtain some indication of the variability in response.
- Biological markers, such as FEV_1, could potentially be used to examine the variability of lung function response to the same chemical exposure in a group of workers over time.
- As animal data are not appropriate to investigate variation in human toxicodynamics, the development of *in vitro* tests using human tissue samples should be considered to provide data to help bridge the knowledge gap in this area.

BODY WEIGHT

- The body weight default values should be reviewed by determining the current range of body weights for male and female workers of various age groups. Up-to-date information is available in the literature but needs to be compiled and analysed. Ranges of body weight and their use in risk assessment need to be considered.

LUNG FUNCTION, ASTHMA, ATOPY AND DERMATITIS

- The prevalence of asthma and atopy in the working population should be monitored by means of a longitudinal investigation to determine whether the increase of 10–15% and 40–50%, respectively, that has been predicted is real, and not a result of improved diagnosis and increased reporting.
- Lung function should be examined in older (currently post-retirement) age groups to determine whether this would be an issue in an ageing workforce. The existing norms are largely based on extrapolation from younger populations and may not be accurate for older age groups.

ALCOHOL

- Existing occupational data should be reviewed, targeting, initially, workers exposed to organic solvents, to investigate the interaction between alcohol and exposure to chemicals.
- A biomarker for long-term alcohol intake levels could be developed to assist the study of potential interactions between alcohol and chemicals in workers.

MEDICATION

- A survey should be conducted to determine the range and amount of prescribed and recreational drugs currently being used by the UK working population*.

* The provision of information by General Practitioners to workers exposed to chemicals in the workplace should be reviewed.

PREGNANT WOMEN AND NURSING MOTHERS

- Existing animal data should be reviewed to determine whether, in general, pregnant animals are more sensitive to chemicals than their non-pregnant counterparts.

AGE AND FUNCTIONAL RESERVE

- There has been a suggestion that occupational exposure to a range of commonly used organic solvents may result in central nervous system dysfunction post-retirement. In order to explore this further it may be appropriate to conduct a follow-up study of retired solvent-exposed workers for any evidence of neurobehavioural or other nervous system-related changes.

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VARIABILITY AND SUSCEPTIBILITY IN HUMAN RESPONSE TO OCCUPATIONAL EXPOSURE TO CHEMICALS IN THE UK

LEICESTER, 6–8 FEBRUARY 2001

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