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Consultation on guidelines for metals and metalloids in ambient air for the protection of human health

May 2008

Department for Environment, Food and Rural Affairs
Nobel House
17 Smith Square
London SW1P 3JR
Telephone 020 7238 6000
Website: www.defra.gov.uk

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Environment in Northern Ireland**

Expert Panel on Air Quality Standards

Guidelines for metals and metalloids in ambient air for the protection of human health

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Terms of Reference

The Expert Panel on Air Quality Standards was established in 1991. The terms of reference of the Panel are:

“To advise the Secretary of State for Environment, Food and Rural Affairs, Scottish Ministers, the National Assembly for Wales and the Department of the Environment (Northern Ireland) as required, on non-occupational ambient air quality standards, with particular reference to the levels of airborne pollutants at which no or minimal effects on human health are likely to occur;

i. taking account of the best available evidence of the effects of air pollution on human health and of progressive development of the air quality monitoring network; but

ii. without reference to the practicality of abatement or mitigation measures, the economic costs and economic benefits of pollution control measures or other factors pertinent to the management rather than the assessment of risk;

Where appropriate, for example for pollutants where no threshold for adverse effects can be determined, the Panel may wish to recommend exposure-response relationships or other information Government might use to set policy objectives.

to identify gaps in the knowledge needed for standard setting and suggest potential priority areas for future research;

to advise on other aspects of air quality and air pollution referred to it;

for the purpose of informing the development of policy on the improvement of air quality and increasing public knowledge and understanding of air quality issues.”

EPAQS does not give approval for products or equipment.

Membership of the Panel

Chairman

Professor Stephen Holgate BSc, MD, DSc, FRCP, FRCPPath, FRCPE, FIBiol, FmedSci, FRSA
University of Southampton

Members

Professor H Ross Anderson MD, MSc, FFPH
St George's Hospital Medical School

Dr Peter Baxter MD, MSc, FRCP, FFOM
University of Cambridge

Dr Paul Cullinan MD, MSc, FRCP, FFOM
Imperial College (National Heart and Lung Institute)

Professor Dick Derwent OBE, MA, PhD
rdscientific

Dr Jonathan Grigg BSc, MD, MRCP, FRCPCH
University of Leicester

Professor Roy Harrison OBE, BSc, PhD, DSc, FRSC, CChem, FRMetS, Hon MFPH, Hon FFOM
University of Birmingham

Professor Frank J Kelly BSc, PhD
King's College London

Dr Geoffrey H Pigott BSc, PhD
AH Marks & Co Ltd

Dr Alison Searl BSc, MSc, PhD
Institute of Occupational Medicine, Edinburgh

Mr John Stedman BA
NETCEN (part of AEA Technology plc)

Ex officio member – Chairman of the Committee on the Medical Effects of Air Pollutants

Professor Jonathan G Ayres BSc, MB BS, MD, FRCP, FRCPE, FFOM
University of Aberdeen

Ex officio members – Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Professor Peter Blain PhD
Newcastle University

Professor David Shuker BSc, ARCS, PhD, DIC, CChem, FRSC
Open University

Lay member

Ms Ann Davison BA

Observers

Mrs Elanor Ball BSc, MSc
Health and Safety Executive

Ms Joan Forteath BEng, MSc, Mphil (observer until September 2004)
Scottish Environment Protection Agency

Mr Colin Gillespie (Observer from September 2004 to January 2008)
Scottish Environment Protection Agency

Dr Colin Powlesland BSc, MSc, PhD
Environment Agency

Assessors

Mr Ronnie Alexander
Welsh Assembly Government

Dr A Branding PhD (assessor until October 2004)
Scottish Executive

Ms Joan Forteath BEng, MSc, Mphil (assessor from October 2004)
Scottish Executive

Mr Ivan Gregg
Department of the Environment in Northern Ireland

Secretariat

Ms Ingrid Holmes BSc, MSc (secretariat from September 2004 to May 2005)
Department for Environment, Food and Rural Affairs

Dr Sarah Honour BSc, MSc, PhD
Department for Environment, Food and Rural Affairs

Professor Robert L Maynard CBE, BSc, MB, BCh, MRCP, FRCPath, FFOM
Department of Health

Dr Martin Meadows BSc, PhD, Cbiol, MIBiol (secretariat to February 2005)
Department for Environment, Food and Rural Affairs

Dr Heather Walton BSc, Dphil (secretariat to February 2005)
Department of Health

Dr Martin Williams BSc, PhD, FRSA
Department for Environment, Food and Rural Affairs

Mr Tim Williamson BSc, MSc, MScienv (secretariat from February 2005)
Department for Environment, Food and Rural Affairs

Preface

The Expert Panel on Air Quality Standards (EPAQS) has reviewed its role in light of the Royal Commission on Environmental Pollution's 21st report *Setting Environmental Standards*¹ and the growing practice of separating risk assessment from risk management. EPAQS' role is to advise on the impact levels of air pollution have on human health. Specifically, EPAQS' terms of reference are to advise on 'the level of airborne pollutants at which no or minimal effect on human health are likely to occur'. The risk management process is undertaken elsewhere. In particular, the Environment Agency uses EPAQS guideline values for minimal or no observable effects in its regulation to ensure that 'no significant pollution is caused'.

¹ RCEP (1998). *Setting Environmental Standards*. Twenty-first report of the Royal Commission on Environmental Pollution. The Stationery Office, London.

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Chapter 1

Introduction

1.1. Background to the report

1. This is the second report by the Expert Panel on Air Quality Standards (EPAQS) as part of a new work programme in which the Panel is advising the Environment Agency (EA) on some of the priority substances that it is responsible for regulating. These reports differ from previous EPAQS reports in that the guideline values they recommend are not intended for use in national air pollutant standard setting.
2. In the past, EPAQS has made recommendations to Government on non-occupational ambient air quality standards for pollutants of national occurrence and importance. Pollutants considered under this new work programme warrant special consideration for their emissions from a small number of point industrial sources and the guideline values are intended to protect local populations around these sites.
3. These guideline values represent a level in ambient air at which no or minimal effects on human health are likely to occur. They are intended for use in the risk assessment of emissions arising from normal operating conditions. Separate guidelines are in place to deal with large releases during chemical incidents. Further information on the control and assessment of major accidental releases can be found on the Health and Safety Executive website at <http://www.hse.gov.uk/hid/index.htm>.
4. In this report EPAQS recommend guideline values for arsenic, beryllium, chromium and nickel. In the environment chromium can occur in two forms, known as chromium (III) and chromium (VI) and it is chromium (VI) that is most toxic and is of concern here. These metals are all human or suspected human carcinogens and have been shown to affect human health through the inhalation route. They are also amongst the substances most frequently encountered by the EA when determining permits for major industrial activities.
5. The World Health Organisation (WHO) have proposed unit risk coefficients for all these substances except beryllium. Indeed there are no national or internationally recognised air quality standards for beryllium. In the past the EA has not used air quality standards derived from unit risk coefficients such as those proposed by the WHO because of the inherent uncertainty involved in extrapolating from observed effects at high levels of exposure to responses at the much lower concentrations commonly associated with environmental exposure.
6. The 4th Air Quality Daughter Directive² sets target (non-mandatory) air quality standards for arsenic and nickel to be met by 31st December 2012.

² Directive 2004/107/EC relating to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air. Official Journal of the European Union L23/3 - 16. 26.1.2005.

However, these target values have been through a process of decision making between member states and it is not clear to what extent they represent a level at which no or minimal effects on human health are likely to occur. In the light of these uncertainties EPAQS were asked to consider setting air quality guideline values for these four metals.

1.2. General issues

1.2.1 Approaches to setting standards

7. The section below outlines the general approach taken by EPAQS when setting standards. It is intended only as a summary. The EPAQS has published a more detailed paper on the standards setting process on its website and the reader is referred to this document (EPAQS, 2003) and to Appendix 1 of this report for more detail.
8. The EPAQS is asked to recommend standards for air pollutants in ambient air that, if met, would be expected to protect the great majority of exposed individuals from adverse effects. Ideally anybody exposed, even for a long period, to air containing pollutants at or below the levels recommended by the standards should be completely protected, i.e., should not experience any ill effects to their health. Such a high level of protection is, in practice, difficult to provide. People vary in their sensitivity to air pollutants: some individuals are particularly sensitive and only very low levels of pollutants would be entirely without effect on them (see Section 1.2.4 for a discussion of susceptible groups).
9. For most substances a standard is set by first identifying a level of exposure at which no adverse health effects have been identified. This is termed a no observed adverse effects level or NOAEL. In cases where there is insufficient data to set a NOAEL, a lowest observed adverse effects level (LOAEL) can be identified instead and a safety factor applied to account for the additional uncertainty in using this as a starting point.
10. Once a NOAEL (or LOAEL) has been identified, safety factors, also termed uncertainty factors, are used to account for inter species differences and susceptible groups in humans in the data from which the air quality standard or guideline is set. These provide a margin of safety between the NOAEL / LOAEL derived from measurements of a small number of humans or animals and permissible levels of exposure for the whole population. Expert judgement is used to determine the number and size of safety factors to be applied. For the metals covered in this report, three human health end points (lung cancer, irritation / inflammation and hypersensitivity) were thought to have specific implication for the applications of safety factors. These considerations are outlined in Section 1.4.2.
11. Where effects arise as a result of prolonged exposure, it is appropriate to adjust the exposure data to allow for continuous exposure in ambient air. An additional factor may therefore need to be applied where the original study from which the NOAEL / LOAEL was derived was not for an entire lifetime, for example from occupational data where people were only exposed at work.

12. The idea that complete protection can be offered by a standard implies that there is a threshold of effect for the pollutant being considered – a level below which normal health is not affected. Although for many substances the concept of a threshold seems to be broadly true, there are some chemicals for which no threshold of effect exists. This group includes genotoxic carcinogens. These compounds are known to cause cancer as a result of interacting with DNA – the material inside the nucleus of cells that carries genetic information.
13. For substances, such as genotoxic carcinogens, where no threshold has been observed for adverse effects, EPAQS uses a similar approach to that it has taken to substances with a threshold. The Panel identifies a starting point at which it believes the risks associated with that exposure are exceedingly small. Safety factors are then applied to this value in the usual way. A broader discussion of the approach used by EPAQS and other organisations in setting air quality guidelines for chemical carcinogens can be found at Appendix 1.
14. An alternative approach to that adopted by EPAQS, and one used by the WHO and some other countries is based on quantitative risk assessment. This approach seeks to extrapolate the occupational data to lower concentrations and therefore to quantify the additional risk of cancer at concentrations likely to occur in the environment. There are many ways in which this extrapolation can be made depending upon the assumed mechanism of carcinogenesis. It should be noted that quantitative risk estimates should not be regarded as being equivalent to the true cancer risk, but represent plausible upper bounds which may vary widely according to the assumptions on which they are based (WHO, 2000). Quantitative risk assessment gives a unit risk factor which can be used to calculate the concentrations of an airborne pollutant associated with a particular level of excess lifetime risk.
15. The quantitative risk assessment method uses the same occupational cancer data as a starting point and inherently very similar assumptions to the EPAQS method. However, unlike the EPAQS method it does not arrive at a single concentration as a guideline. Rather, it is necessary for the standard setting agency to specify a maximum tolerable level of risk which can then be converted to a guideline concentration using the unit risk factor.

1.2.2 Additional uncertainties

16. There are a number of uncertainties in the standards setting process that are not formally accounted for in the use of safety factors. An example is the uncertainty associated with the assessments of exposure to a pollutant in the original occupational or epidemiological study, which may not have been well measured. Extrapolation from occupational workers to the general population has other uncertainties due to possible differences in the chemical or physical form of the pollutant and/or the pattern of exposure. These uncertainties can lead to either an over- or an under-estimate of the overall toxicity of a substance, however, given the uncertainties of, for example extrapolating from animals to humans, the additional uncertainty is likely to be small.

17. Although not formally assessed through the use of safety factors, these additional uncertainties are taken into account when evaluating the overall quality of the evidence on which a NOAEL / LOAEL is based and the precautionary way in which safety factors are applied.

1.2.3 Exposure to multiple pollutants

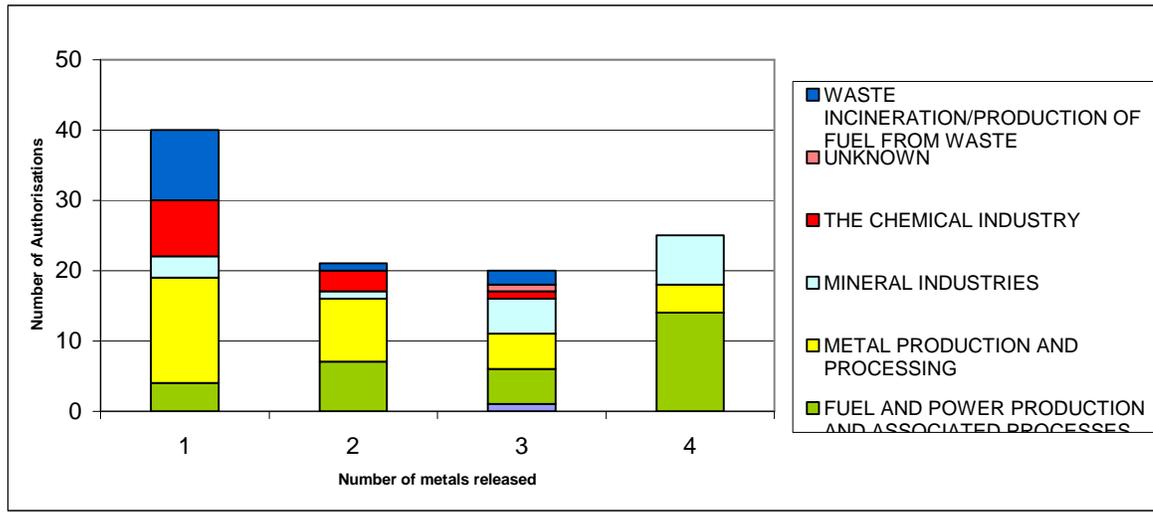
18. Individual industrial processes may release a wide variety of pollutants, which can include a number of the metals and metalloids considered in this report. Of these substances, chromium and nickel are the two main metals released. In the case of chromium the metals industry is the major source, whereas nickel arises mainly from the burning of fossil fuels, although a substantial proportion does also come from the metals industry. Table 1.1 shows the releases of these metals from different industrial sectors regulated by the EA in England and Wales. It should be noted that the EA's Pollution Inventory does not distinguish between the two different forms of chromium (chromium (III) and chromium (VI)).

Table 1.1: Releases of arsenic, beryllium, chromium and nickel from industry sectors reported in the Environment Agency's Pollution Inventory for 2005. (Zero indicates all reported data below reporting threshold)

Industry Sector	Arsenic (kg)	Beryllium (kg)	Chromium (kg)	Nickel (kg)
Animal, vegetable and food	4	0	16	18
Fuel and power	616	96	3,617	10,191
Metal production	191	6.8	4,830	3,716
Mineral production	73	20	1,089	420
Other industry	0	0	0	0
Paper, pulp and board	0	0	0	0
Sewage treatment works	0	0	0	0
Sites handling radioactive substances	0	0	0	0
Chemical industry	18	<0.1	7,161	1,151
Unknown	5.6	0	19	49
Waste disposal and recovery	0	0	0	0
Waste incineration/production of fuel from waste	12	0	342	42
Waste landfill	0	0	0	0
Total – all industries	922	123	17,076	15,587

19. A slightly different picture emerges if the number of activities which release these substances are considered. Of the 106 activities that released these metals above the reporting threshold in 2005, 40 released only a single metal, whilst 25 released all four. Figure 1.1 shows the number of activities regulated by the EA in England and Wales which co-release the different metals. The major source of all four metals together is the fuel and power sector. The sector with the next highest number of activities which release all four metals is the mineral industry, although it is the metals sector which releases the greater quantity.

Figure 1.1: Number of activities regulated by the Environment Agency which release arsenic, beryllium, chromium and nickel to air (2005 data).



20. In this report, the effects of individual pollutants have been considered separately. However, the Panel recognises that ambient air that includes localities around an industrial plant contains a complex mixture of pollutants at differing concentrations. The effects of exposure to more than one pollutant may be additive (i.e., the sum of the individual pollutant effects), synergistic (i.e., greater than the sum of the individual pollutant effects) or antagonistic (i.e., less than the sum of the individual pollutant effects).
21. There is a paucity of information on the patterns of exposure of populations to various mixtures of pollutants and on the effects of these mixtures. Whether effects are additive, synergistic or antagonistic will depend on the pollutants involved, their likely mechanisms of effect and their concentrations.
22. In general, the default assumption is that the effects of multiple pollutants are additive unless there is evidence to the contrary.
23. Much of the information on the harmful effects of metals on humans comes from studies of populations whose exposures have occurred at work. Where there is exposure to more than one toxic metal then it may be difficult to distinguish the effects of one from the other; the same is true for simultaneous exposures to other harmful substances such as noxious fumes at work or, commonly, cigarette smoke. Failure to account for such 'confounding' exposures may lead to an overestimate of the risk attributed to the metal under study.
24. The application of guideline values is outside the scope of the Panel's remit. However Agencies making use of these recommendations should be aware that in deriving recommended values, the Panel considered each of the pollutants in isolation. It is recognised that there are similarities in the range of effect seen for each of the individual metals considered. For some responses, notably hypersensitivity, the individual

metals are unlikely to show cross-reactivity but in other cases, for example when an irritant effect is seen, responses can be anticipated to be additive. These factors should be taken into account by external Agencies when applying the values in environments where mixed exposures are likely. The Panel recommends that in case of doubt a precautionary approach is appropriate.

1.2.4 Susceptible and vulnerable groups

25. Children are at increased risk of adverse health effects from any inhaled toxin. The factors that contribute to this increased vulnerability are discussed in detail in Appendix I of the Halogens and Hydrogen Halides report (EPAQS, 2006a). In general, children spend more time outdoors, tend to be more active, and have higher ventilation rates than adults. All of these factors increase the lung dose of an inhaled toxin. For the metals addressed in this report, the integrity of the lung's antioxidant defences may also be important. Whether lung antioxidant defences in the paediatric lung are impaired, remains unclear. Lung tissue analysis shows that messenger RNA levels for the antioxidant enzymes manganese and copper-zinc superoxide dismutase are lower in children, but this does not appear to be associated with reduction in function (Asikainen *et al.*, 1998). At the other end of the age spectrum, it has been hypothesised that an imbalance between oxidant and antioxidants in the lung contributes to the development of chronic obstructive pulmonary disease (COPD) (Macnee, 2007). Patients with COPD, and other chronic lung conditions associated with airway inflammation, may therefore be more susceptible to inhaled "pro-oxidant" metals. Since there is uncertainty whether healthy children and patients with chronic respiratory diseases represent susceptible groups for metals inhalation, a correction factor has been applied to take this uncertainty into account.

1.2.5 Units of concentration and choice of averaging times

26. In this report pollutant concentrations are measured as the mass of a pollutant in a standard volume of air, usually a cubic metre. This is because the metals and metalloids being considered are mainly found as particles suspended in the air (see paragraph 34) and not as gases. Box 1 gives more information on units of mass, concentration and particle size.

27. When recommending an averaging time for a guideline value, the Panel takes into account a number of considerations (see EPAQS, 2006b). The most important of these is the length of exposure thought to give rise to the health effect of concern. For example, some substances, such as sulphur dioxide, have irritant effects that are almost instantaneous and for these chemicals a short averaging time of an hour or less are recommended. For other pollutants where the effects on health are thought to be due to longer-term, chronic exposure, an averaging period of one year is generally chosen. This is the case for the metals considered in this report, with the exception of beryllium, where the human health endpoint thought to occur at the lowest concentrations is

carcinogenicity. Further justification for the choice of averaging time is given in the individual chapters.

Box 1: Units used to express the concentration and size of particles in air

Units of concentration

Mass (how much something weighs) is measured in grams. A milligram (mg) is one thousandth of a gram, a microgram (written μg) is one millionth of a gram and a nanogram (written ng) is one billionth of a gram. As a rough guide a grain of granulated sugar is approximately 1 mg and a grain of milled white pepper about one $1 \mu\text{g}$.

Volume is measured in cubic metres (written m^3). A cubic metre is equivalent to 1000 litres.

Particle concentrations are measured as the mass of a pollutant in a standard volume of air. Concentrations of air pollutants are generally very low and therefore the units of mass used are very small. In this report concentrations are written as milligram per cubic metre, that is mg/m^3 , micrograms per cubic metre, that is $\mu\text{g}/\text{m}^3$, or nanogram per cubic metre, that is ng/m^3 .

Particle size

Particles are found in a range of sizes, however, it is only particles that are likely to be inhaled into the lung that are of interest when considering health effects. Particle size is generally measured in micrometers (written as μm), one micrometer is a millionth of a metre.

These 'inhalable' particles, are defined as having a diameter of less than $10 \mu\text{m}$ and can be divided into coarse particles, with diameters ranging from $2.5 \mu\text{m}$ to $10 \mu\text{m}$ and fine particles with diameters equal to or less than $2.5 \mu\text{m}$. As a rough guide, the average human hair is $70 \mu\text{m}$ in diameter, making it 7 times larger than the largest coarse particle.

Particles with a diameter of less than $10 \mu\text{m}$ can also be referred to as PM_{10} .

1.2.6 Development of the report

28. In order to facilitate the development of guideline values for a large number of compounds, the EA provided EPAQS with a dossier on each of the substances under consideration. The dossiers included:

- a review of relevant animal toxicity data;
- a review and preliminary evaluation of existing literature on human toxicology and health effects;
- a review of evaluations and recommendations by other authoritative bodies.

29. These dossiers have been published as EA Research and Development Reports and are available on the Agency publications website (<http://publications.environment-agency.gov.uk>).
30. The EPAQS used the dossiers to provide background information and as an aid to identifying the key studies on which to base their recommendations. When appropriate, members of the Panel went back to the original papers and supplemented these with additional research of their own. Air quality guideline values were reached through reviewing the available literature and the application of expert judgement.

1.3. How the Environment Agencies will use the guideline values

31. The European Union Integrated Pollution Prevention and Control Directive applies an integrated environmental approach to regulating industrial emissions from specified installations. This has been implemented in the UK through the Pollution Prevention and Control Regime and from April 2008 will be taken forward by the Environmental Permitting regime.
32. Under this legal framework the EA regulates approximately 4,000 of the potentially most complex and polluting industrial installations in England and Wales with many smaller installations being regulated by local authorities. The situation is slightly different in Scotland where the regulator, the Scottish Environmental Protection Agency, regulates all installations covered by the regime. The Northern Ireland Environment and Heritage Service is the environmental regulator for Northern Ireland.
33. The Environmental Permitting regime applies the principles of Integrated Pollution Prevention and Control (IPPC), requiring the regulator to ensure that 'no significant pollution is caused' and that conditions are included in the permit, subject to the application of the Best Available Techniques (BATs) that:
 - ensure a high level of protection for the environment as a whole;
 - have regard to the potential to transfer pollution from one environmental medium to another;
 - take account of an installation's geographical location and local environmental conditions;
 - are aimed at minimising long distance and transboundary pollution;
 - ensure appropriate protection of the soil and groundwater.

The Environmental Permitting regime uses some different terms, for example, BAT is referred to as appropriate measures. This is presentational as Environmental Permitting includes waste management sites not subject to IPPC. For those sites subject to IPPC all the requirements of this directive remain in place.

34. To gain a permit, operators will have to show that their proposals represent the BAT to prevent and minimise pollution from their installation. In order to assess the environmental impact of an installation

or identify the BAT from a range of options, the EA in conjunction with the Scottish Environment Protection Agency and the Environment and Heritage Service has developed an assessment methodology known as H1: Guidance on Environmental Assessment and Appraisal of BAT. Operators are not required to use the methodology when making their application for a permit but it does provide a structured assessment process which addresses the specific requirements of IPPC. Operators using an alternative approach would need to ensure that an equivalent level of assessment is made.

35. The H1 methodology consists of the following basic steps:
 - Define the objective and scope of assessment.
 - Generate options of techniques to control pollution.
 - Assess the environmental impacts of each option.
 - Evaluate the costs to implement each option.
 - Identify the option which represents the best available technique.
36. Environmental criteria are used within H1 primarily to:
 - assess the significance of releases to different environmental media and to screen out insignificant effects;
 - assess the relative effects of releases within and between different environmental media.
37. However, there are relatively few established environmental criteria that are suitable for use within the assessment methodology. For example, EPAQS have published standards for nine of the major air pollutants and six other pollutants. The WHO has set guideline values for 14 organic and 15 inorganic pollutants, including some for which standards have also been set by EPAQS. Overall, recognised air quality standards are available for only approximately 37 different substances. This is to be compared with the 129 substances that are reported as being released to the air from industrial installations on the EA's Pollution Inventory and on the Scottish Environment Protection Agency's Scottish Pollutant Release Inventory.
38. In order to fulfil its regulatory role, the EA has developed environmental criteria known as Environmental Assessment Levels (EALs) for different environmental media (air, water and land) for use within the H1 framework. A hierarchical approach has been used to develop EALs. For air, existing standards and guidelines are used as EALs; however, as there are only a limited number of appropriate values, EALs for most substances have been derived from occupational exposure values by the application of a simple safety factor (EA, 2003). The air quality guidelines proposed by EPAQS in this report, and their previous report on halogens and hydrogen halides, will replace these less robust values for use within the H1 methodology.

In using the guidelines, it is appropriate for the EA to take into account particular public concern in the case of carcinogens. This is well evidenced, for example by the fright or outrage factors published by the Department of Health (1998).

1.4. Introduction to the metals and metalloids

1.4.1 Physio chemical characteristics

39. In this report EPAQS recommends air quality guideline values for four metals and metalloids³: arsenic (As), nickel (Ni), chromium (Cr) and Beryllium (Be).
40. Almost all of the metals and metalloids present in the atmosphere are present there as suspended particulate matter. The main exception to this is mercury, of which the most abundant form in the atmosphere is elemental mercury vapour. Arsenic forms a gaseous hydride, arsine, but these such cases are relatively rare. Much of the atmospheric metal and metalloid particulate matter derives from human activities and is found in the fine and coarse particle size ranges.
41. Metals and metalloids in ambient air may be present in many different chemical forms and these differences may affect not only their behaviour in the environment but also their behaviour once inhaled or ingested. They may be present as their elemental forms, that is to say not combined with other elements into simple compounds, or be combined as oxides, carbonates or sulphates. They may be present as single compounds or as mixtures of compounds. Many metals and metalloids form a series of compounds with the same element. In that case, the metal or metalloid would be said to exhibit different oxidation states and arsenic is a good example of such a metalloid. Physico chemical and toxicological properties may change markedly between these different oxidation states.
42. Particulate metals and metalloids in the atmosphere show a wide diversity of chemical forms because of their presence in different compounds in different oxidation states. This diversity is generally caused by the different emission sources which are often specific sources of specific compounds. Coal combustion tends to produce metal and metalloid oxides in their highest oxidation states. Atmospheric chemical processes may also change the chemical nature of the metal or metalloid after emission to the atmosphere. It is plausible for industrial and occupational exposures to involve different chemical forms of metals and metalloids when compared with ambient exposures, however this diversity of chemical forms is not apparent from ambient measurements which almost always report the total metal or metalloid content of the particulate matter independent of its chemical form.

1.4.2 Key human health effects and their influence on safety factors

43. There are three effects which are common to some or all of the pollutants considered: lung cancer, irritation / inflammation and hypersensitivity (allergy). When considering each effect the Panel applied the following principles in the application of safety factors.

³ An element which is intermediate of metals and nonmetals in terms of malleability, ductility, conductivity and lustre.

1.4.2.1 Lung cancer

44. The panel considers that the mathematical extrapolations used by some Agencies (particularly the USA Environmental Protection Agency and WHO) to be insufficient as the sole determinants of guideline values for the UK. This reflects concern over the high uncertainty associated with extrapolation well beyond available data, the high dependence of the derived value on the maximum concentration tested/measured and the lack of public debate and acceptance in Britain of the way in which risk values derived in this way should be interpreted and applied. Thus, while these extrapolations informed the decisions taken, they were not definitive. The panel used the following approach.
45. Where good quality epidemiological data were available, these were used as the primary source. If a clear no-effect level could be derived then this was the starting point for extrapolation. In most cases this was not available and residual doubt remained even at the lowest exposure levels. Also there were frequently fewer measurements at lower than at higher exposure levels. It is recognised that the actual exposures in these groups are often underestimated so that the recorded level contains an inbuilt "safety" factor. Nevertheless, in these circumstances the Panel applied an additional factor as a precautionary measure. The size of the factor was determined by the magnitude of potential "effect" at the exposure level selected, the nature of the dose-relationship established at higher levels and the measurement uncertainty in the value adopted, but the default was a factor of ten.
46. In addition, a further factor was applied when the values were derived from occupational exposures. The general public is exposed to polluted air for 24 hours a day, 365 days a year for a lifetime (taken as 70 years) whilst the occupationally-exposed worker will be exposed only for about 220 working days per year, 40 hours per week for a 40 year maximum working lifetime. This led to an exposure duration safety factor of ten. A further factor of ten was applied as a precautionary measure to reflect possible differences in susceptibility in the population as a whole compared to workers. This is arguably not applicable as not all workers exposed to carcinogens develop the disease. It could be assumed that those who do contract the disease represent a "susceptible population" and there is no reason to assume that these individuals are differentially represented in workers compared to the general public. Nevertheless as the Panel has consistently adopted a precautionary approach to standard setting, this factor was applied.
47. Where there are good animal models of disease and high quality experiments on which to base a decision the approach adopted was similar, except that an additional factor of ten was applied to allow for possible differences in susceptibility between humans and experimental animals. The "exposure factor" was adjusted to reflect the regimen used in the animal study (continuous exposures at constant concentration are often used, with young animals exposed at the beginning of the study so an additional factor may not be required)

1.4.2.2 Irritation/inflammation

48. This effect is usually modelled in animals as there is seldom significant systematic histological evaluation of human tissue. However, supplementary physiological information from human studies is used when available and can be definitive when these reactions are known to be the most sensitive index of response.
49. When animal data are used, the nature of the response determines the “first” factor to be applied. When this is irritation of the respiratory tract with no (or marginal) histological reaction then a factor of two to four may be applied to a NOAEL as a precautionary measure. This reflects the high level of confidence that these effects are unlikely to be more severe in humans than in animals. Where a minimal effect level is used for extrapolation an additional factor is applied as described in the “lung cancer” section. For respiratory irritation this factor may be at the level of two to four, again reflecting the significant information available to model this response and the relatively minor nature of the response in humans (ranging from “a tickle in the throat” to a cough at levels just above the no-effect threshold). For more severe effects such as chronic inflammation, a factor of ten would be more usual.
50. A further factor of ten is applied to animal data or to the NOAEL derived from human responses to reflect possible differences in susceptibility in the population as a whole. This factor may be reduced or eliminated if the data were derived from a susceptible group, for example, asthmatics.

1.4.2.3 Hypersensitivity

51. This response is usually induced by intermittent contact at high level. In contrast, continuous exposures, even at high levels, may protect against the development of allergy through the induction of immunological tolerance. Once sensitised an individual may respond to concentrations very much lower than those necessary to induce the initial reaction. There is only limited evidence for cross-reactivity between dermal and inhalation exposures, but it is reasonable to assume that this may be possible for soluble materials in sensitised individuals.
52. The Panel considered that the guideline values adopted for pollutants should prevent the development of hypersensitivity. The Panel did not consider it realistic to allow for idiosyncratic responses which could nonetheless be possible in a few individuals with extreme sensitivity. However, where available, literature values for the threshold of response were examined to assure that guideline values would not provoke a reaction in sensitised individuals. The values derived are considered to fulfil this requirement, with values well below those known to provoke reactions.

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Chapter 2

Arsenic

2.1 Background

2.1.1 Basic chemical information

53. Arsenic is one of those chemical elements known as a metalloid, which reflects the fact that it exhibits properties intermediate between those of the metals and the non-metals. It occurs naturally in the environment within the earth's crust, having a relatively low average abundance of around 5 mg/kg. Its distribution is, however, uneven and there are some locations, most notably Bangladesh, where high naturally occurring concentrations can leach into groundwater, posing a serious human health risk.
54. Arsenic can exist in four oxidation (valence) states, summarised in the Table below:

Table 2.1: The different oxidation states of arsenic.

Oxidation state	Chemical name
0	arsenic (free element)
-3	arsine
+3	arsenite (AsIII)
+5	arsenate (AsV)

Within the gas arsine (AsH_3) arsenic is in the -3 oxidation state; the free element (0 oxidation state) is very unlikely to be observed in the environment. Most commonly arsenic is in the environment in its $+3$ oxidation state as arsenite – abbreviated to As(III) - or in combination with other elements such as chlorine and sulphur, or as arsenate ($+5$ oxidation state) – abbreviated to As(V). Arsenic in the atmosphere is most commonly present as mixtures of arsenites and arsenates. The proportion of As(III) to As(V) varies from 27% to over 50% (European Commission, 2000). Because of the relatively high vapour pressure of certain As(III) compounds such as arsenic trichloride, arsenic is present both as vapour and particles in the atmosphere.

55. At one time there was major use of arsenic in pesticides and this continues in the form of copper chrome arsenate used as a timber treatment. Other uses include incorporation in metal alloys. Because of its presence in the earth's crust, arsenic exists in a range of crustal materials including coal and metal ores and consequently can be released to the atmosphere during their combustion or processing.

2.1.2 Sources of arsenic in the UK atmosphere

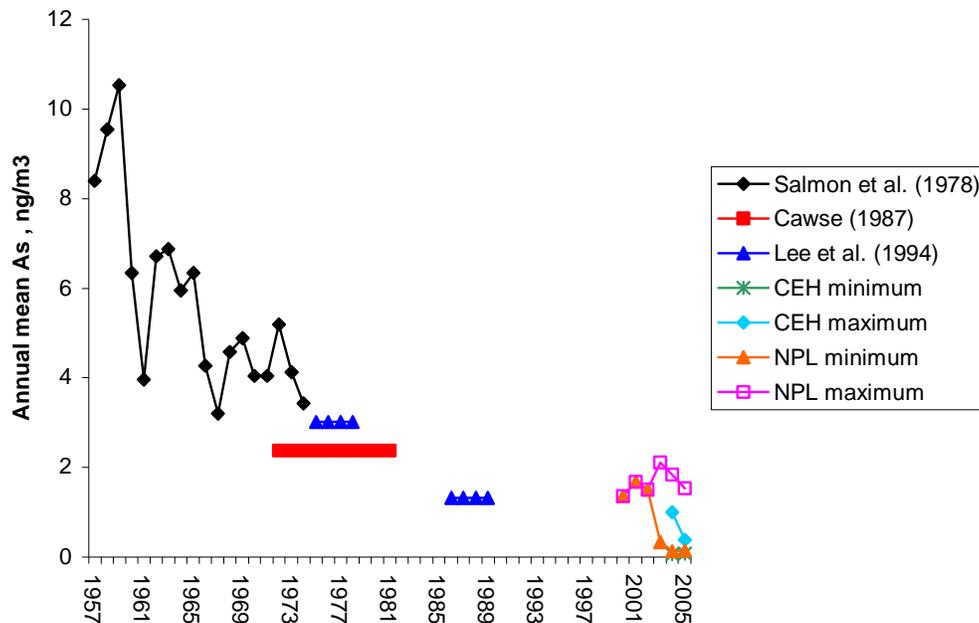
56. Arsenic is primarily emitted into the atmosphere by high-temperature processes such as coal-fired power generation, smelting, burning vegetation and volcanoes (WHO, 2000). Natural low-temperature biomethylation and microbial reduction also release arsenic into the atmosphere; microorganisms can form volatile methylated derivatives of arsenic under both aerobic and anaerobic conditions, and can reduce arsenic compounds to release arsine gas (Cheng and Focht, 1979; Tamaki and Frankenberger, 1992).
57. Arsenic is released into the atmosphere primarily as arsenic trioxide (As_2O_3) or, less frequently, as one of several volatile compounds, arsines. Arsenic released to air exists mainly in the form of particulate matter (Coles *et al.*, 1979). These particles have a lifetime of up to 10 days before removal by wet and dry deposition and readily undergo long-range transboundary transport (USEPA, 1984). Arsines that are released from microbial sources in soils or sediments undergo oxidation in the air, reconvert the arsenic to less volatile forms that are removed by wet and dry deposition (Parris and Brinckman, 1976).
58. Historically, the main source of arsenic emissions to the air in the UK has been the combustion of coal in power stations, industry and for domestic heating (Dore *et al.*, 2006). The main sources reported in the UK National Atmospheric Emissions Inventory for 2004 include emissions from the combustion of treated wood and combustion of coal in industry and power stations. Combustion of coal in power stations, industry and for domestic heating contributed 10% of the national total in that year. Combustion of fuel oil at refineries, in industry and from shipping contributed 7%. Emissions from the combustion of wood treated with copper-chromium-arsenic preservatives were estimated to contribute up to 50%, although this estimate is uncertain. Emission from metal industry sources make up a relatively small percentage of total UK emissions (7%) but may constitute the most important source in the vicinity of specific industrial plants.
59. UK emissions of arsenic are estimated to have declined by 78% between 1970 and 2004 as a result of reductions in the combustion of coal in power stations, industry and for domestic heating.

2.1.3 Ambient concentrations

60. Measured annual mean arsenic concentrations in air in 2005 ranged from 0.1 to 0.4 ng/m^3 at rural locations, 0.8 to 1.4 ng/m^3 at urban locations and 0.8 to 1.5 ng/m^3 at monitoring sites close to metal industries. Concentrations ranged from 0.3 to 8.4 ng/m^3 in 2000, when measurements were made at a larger number of sites (Vincent and Passant, 2006). Concentrations at rural monitoring sites in the UK have declined sharply, reflecting the changes in UK emissions (Conolly, 2003).
61. Figure 2.1 presents the time history of the available rural measurements of total particulate arsenic from 1957 through to 2005. Annual mean levels fell from their maximum levels in the late 1950s to their current

minimum levels. Current levels appear to be about a factor of 30 below their historical levels. In recent years, the figure shows the range of values measured at monitoring sites in the national networks. The highest measured concentrations in urban or industrial areas are similar to or lower than the historical rural concentrations and recent concentrations at rural sites are also lower than historically recorded.

Figure 2.1: Time history of the available annual mean total particulate arsenic concentrations in rural air from 1957 through to 1989 for Harwell, Oxfordshire (Cawse, 1987; Lee *et al.*, 1994; Salmon *et al.*, 1978) and the maximum and minimum values measured in the national monitoring networks from 2000 to 2005 (NPL, 2006; CEH, 2006).



Measurements of the mass size distribution of arsenic in polluted urban and rural air have typically shown a bimodal size distribution. The more abundant proportion is present in fine particles of less than 1 μm aerodynamic diameter (Rabano *et al.*, 1989; Waldman *et al.*, 1991; Kelley *et al.*, 1995) consistent with a source in combustion processes (e.g. power stations) or gas-to-particle conversion of arsenic-containing vapours. The less abundant proportion in the size distribution is in the range of 5-10 μm aerodynamic diameter and probably arises from windblown soils and dusts. In urban emissions the As(III)/As(V) ratio for both fine and coarse particles is approximately 1 (Rabano *et al.*, 1989).

2.1.4 Human Exposures

62. Non-occupational, human exposures to arsenic are incurred through: drinking (ground) water; eating fish (mainly low toxicity organic arsenic species) or food grown in contaminated soils; the use of arsenic-containing compounds such as old types of pesticide, wood

preservatives or some medicines, including 'herbal' types; pica; cigarette smoking; and residence in neighbourhoods with industrial contamination. Most of these are no longer relevant to UK populations. Only the last two sources of exposure involve respiratory exposures. For the general population, inhalation of arsenic from ambient air is a minor route of exposure. In the USA average daily intakes from ambient air are estimated to range from 0.3 to 0.4 ng / kg of body weight / day (ATSDR, 2007), approximately 0.5% of total daily exposure to inorganic arsenic.

63. Levels of arsenic in cigarettes have been greatly reduced by the prohibition of arsenical pesticides in tobacco production. The inhaled smoke from currently available cigarettes contains between 0 and 1.4 µg arsenic per cigarette; this wide range is believed to reflect variations in the field history, soil, and fertilizer conditions under which the tobacco is grown (Smith *et al.*, 1997).
64. Occupational exposures to inorganic arsenic occur during the smelting of non-ferrous ores, especially copper and lead which are frequently contaminated by arsenic; work in some coal-burning power plants and municipal incinerators; the production or use of pesticides or wood preservers that contain the mineral or the sawing or burning of wood preserved in the same way; work in the microelectronics industry (gallium arsenide); and work in cotton harvesting or processing. In each case the primary route of exposure is probably inhalation although oral and dermal routes may also be important.
65. Studies of patients with lung cancer (Holland *et al.*, 1959) and of workers with occupational exposure to inorganic arsenic trioxide (Pinto *et al.*, 1976) suggest that between 30 - 60% of inhaled arsenic is absorbed. There are no human data on the body distribution of arsenic after inhaled exposures, and none to indicate that the fate of inhaled arsenic in children is different from that in adults, although this may not be the case for arsenic imbibed in drinking water (Meza *et al.*, 2005).

2.2 Animal toxicology

2.2.1 Pulmonary Absorption

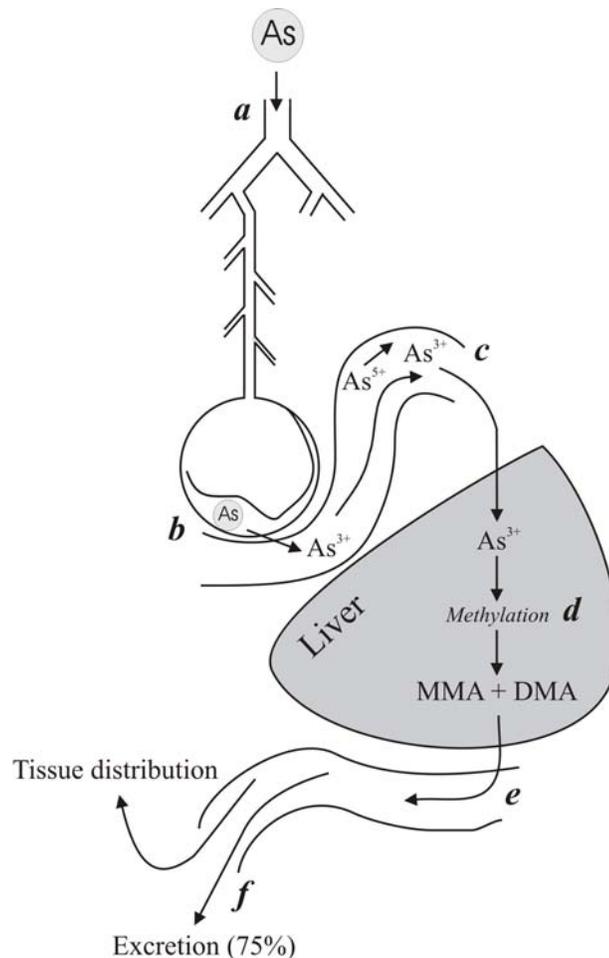
66. Most studies relating to the toxicokinetics of arsenic have been performed in animals. Depending on the chemical form, particle size and solubility, arsenic is readily absorbed from the lungs (Gochfeld, 1995). Absorption of arsenic from the respiratory tract is a two-part process involving deposition of the particles onto airway surfaces and then absorption from deposited particulates. After inhalation of soluble arsenic compounds (for example, arsenic trioxide), most of the deposited arsenic is absorbed into the bloodstream from the digestive tract following respiratory clearance (Marafante and Vahter, 1987). However, particles of low solubility (for example, arsenic trisulphide, calcium arsenate, lead arsenate and gallium arsenide) are retained to a great extent in the lungs (Pershagen *et al.*, 1982; Webb *et al.*, 1984; Marafante and Vahter, 1987). Dissolution of certain arsenic-containing particles, for example, lead arsenate, by alveolar macrophages may increase the rate of

absorption in the lungs (Marafante and Vahter, 1987). Data from mice experiments indicate that continuous inhalation of arsenic causes an increase in tissue levels for a couple of weeks, after which they may decrease in spite of ongoing exposure (Bencko *et al.*, 1973). No explanation was provided for this observation.

2.2.2 Metabolism

67. The metabolism of arsenic has been extensively studied in animals. It consists of two processes: reduction/oxidation reactions that interconvert arsenate and arsenite and methylation (Figure 2.2). These processes are similar whether exposure is by inhalation, ingestion, or by injection with more than 75% of the absorbed arsenic dose being excreted in the urine (Marcus and Rispin, 1988). Arsenic is methylated in the body to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). Methylation takes place mainly in the liver and may be considered a detoxification mechanism for arsenic, since the methylated metabolites have a lower affinity for tissue constituents and lower toxicity than arsenic, especially the trivalent form (Vahter *et al.*, 1983).

Figure 2.2: Arsenic - pulmonary absorption, metabolism, tissue distribution and excretion. (a) 30-60% inhaled arsenic present in most respirable particles is deposited in the lung. (b) Particles deposit onto the airway surface and the soluble forms if arsenic move into the airway fluid. (c) Pentavalent arsenic is reduced to trivalent arsenic in the blood. (d) Trivalent arsenic is taken up by the liver and metabolised to monomethylarsonic acid and dimethylarsinic acid. (e) monomethylarsonic acid and dimethylarsinic acid are eliminated from the liver and excreted by the kidney (f) The majority of inhaled arsenic is excreted by the kidney.



Pentavalent arsenic tends to be eliminated rapidly. It is largely (50–70%) reduced in the blood to the trivalent form, part of which is methylated in the liver (Marafante *et al.*, 1985; Vahter and Marafante, 1985). The efficiency of methylation decreases with increasing dose level and with low protein intake (Vahter and Marafante, 1987).

2.2.3 Tissue distribution and excretion

68. Most forms of inhaled arsenic are excreted within a few days via the kidney as MMA and DMA. Urinary excretion accounts for 30 – 60% of the inhaled dose (Vahter, 1986). Since the deposition fraction of an inhaled dose ranges from 30 - 60% for most respirable particles, this

suggests that nearly all arsenic that is deposited in the lung is excreted in the urine. The relative proportions of arsenic, MMA, and DMA in urine vary depending upon the chemical administered, the time after exposure, the route of exposure, the dose level, and the exposed species of animal. Increased MMA/DMA ratios have also been observed in mice, but only at much higher doses (Hughes *et al.*, 1994).

69. Several pharmacokinetic models have been developed for evaluating the kinetic behaviour of arsenic (Clewell *et al.*, 1999). However they focus on the prediction of the urinary elimination of arsenic species under different exposure conditions, rather than estimation of arsenic species concentrations in the various target tissues associated with arsenic's adverse effects.
70. Although no studies on the distribution of organic arsenic in animals after inhalation exposure were identified, DMA administered to rats via the trachea was distributed throughout the body suggesting that inhalation of organic arsenic compounds also leads to widespread distribution. Where excretion of organic arsenic compounds is concerned it appears to be prompt, rats exposed to DMA via the trachea excreted 60% in the urine and about 8% in the faeces within 24 hours (Stevens *et al.*, 1977).

2.3 Health Effects

2.3.1 Acute effects

2.3.1.1 Animals

71. Aqueous solutions of arsenic are ten times more toxic than arsenic administered dry by the same route. Rats appear more susceptible to arsenic in solution than mice of a similar age, although no difference in acute toxicity was found between males and females of the same species. There are, however, considerable differences in arsenic toxicity among different strains of mice. Following acute administration marked haemorrhage of the stomach and intestine has been reported (Satterlee, 1958) as well as fatty degeneration of the liver with cell necrosis and reparative changes (Rossing, 1941). No reports have been found showing that metallic arsenic has appreciable acute toxicity.
72. Arsenic inhibits the activity of many enzymes involved in energy metabolism, specifically oxidative phosphorylation. This inhibition results in reduced levels of the high energy phosphate molecules that drive many essential reactions in the cell (Squibb and Fowler, 1983) and is reversible. The toxicity of trivalent arsenic can be reduced by the addition of a free thiol (such as glutathione), while thiol depletion increases toxicity (Clewell *et al.*, 1999). Binding of arsenic to dithiols also inhibits energy metabolism and is more difficult to reverse. Pyruvate oxidase, a critical enzyme in energy metabolism, needs a dithiol (lipoic acid) cofactor to produce acetyl coenzyme A, the 'fuel' for oxidative phosphorylation. Pentavalent arsenic is less reactive with tissue constituents, but the arsenate ions can substitute phosphate ions in various enzyme catalysed reactions (Squibb and Fowler, 1983). The similarity of arsenate to phosphate results in the formation of arsenate

esters in place of phosphate. These are unstable, so the process leads to an effective uncoupling of oxidative phosphorylation again inhibiting energy metabolism.

2.3.1.2 Humans

73. All the available human evidence is based on occupational studies, mostly among smelter workers exposed to arsenic trioxide. None appear to relate acute health effects to exposure levels. Death from acute inhalation appears to be unlikely even with exposures up to 100 mg/m³ (ATSDR, 2007). Exposure to arsenic dust causes irritation of the conjunctivae and upper respiratory tract and there are reports of perforation of the nasal septum occurring in a matter of days or weeks. The mechanisms for these effects are unclear.
74. In extrapolating from this limited occupational evidence to the ambient situation, it is important to consider to what extent symptoms occurring in the occupational context are associated with a larger size of arsenic particles than is found in ambient air. Pinto and McGill state that "23% by particle count are greater than 5.5 µm" (Pinto and McGill, 1953) whereas most ambient arsenic is in particles smaller than this. The irritant effects reported in occupational studies may be due to larger size particles deposited in the upper respiratory tract. The European Community (EC, 2000) and Institute for Environment and Health (IEH, 2000) also refer to arsenic causing lower respiratory irritation (bronchitis), but no primary sources for this observation are cited.
75. Published no observed adverse effects levels (NOAELs) for acute exposure vary in size and their rationale. The Health and Safety Commission (HSE, 1986), based on the HSE Toxicity Review 1986 cites a NOAEL of 0.4 to 2 mg/m³ for respiratory irritation. The EC (2000) consider that acute irritant effects are likely to be minimal at exposure levels of about 0.1-1.0 mg/m³. The same levels are suggested by IEH (2000) and CSTE (2001).
76. On the basis of meagre quantitative evidence from occupational studies, there is a consensus that acute irritative effects on the upper respiratory system and conjunctivae are unlikely at exposure levels between 0.1 - 1 mg/m³ of arsenic. It is likely that a greater proportion of ambient arsenic is in the respirable particle range, which might lead to greater toxicity in the lower respiratory tract for a given mass concentration; this needs to be taken into consideration in determining an ambient standard.

2.3.2 Chronic effects

2.3.2.1 Animals

77. Animals appear to be considerably less sensitive than humans to the toxic effects of arsenic. The basis of this difference is not well understood but may involve the metabolic fate of arsenic. For example, in rabbits exposure to inhaled arsenic at levels of 0.05, 0.1, 0.22 or 1.1 mg/m³ for 8 hours a day over 8 weeks led to a significant increase in

plasma inorganic arsenic concentrations at only the two higher experimental exposures (Beck *et al.*, 2002).

2.3.2.2 Humans

78. A large number of adverse human health effects have been attributed to chronic arsenic exposure. In many cases these relate to long-term oral exposures; there are fewer studies of the human toxicity of inhaled arsenic, and almost all of them are of populations exposed in the workplace.
79. Disease associations with arsenic exposure may not be causal if there are simultaneous, confounding exposures to agents such as cigarette smoke or other toxic dusts and fumes. Very few studies have adequately controlled for these. Causal attribution is enhanced if a consistent relationship between arsenic exposures and disease risk has been observed.
80. Non-malignant, non-developmental effects that can potentially be attributed to long-term arsenic exposures include upper airway irritation and nasal septal perforation and conjunctivitis reported from workforces with unquantified but probably very high exposures incurred before 1950 (Lundgren, 1954; Pinto and McGill, 1953). The contributions of potentially confounding exposures were not fully considered. In the absence of control for smoking, reports of increased risk of other non-malignant respiratory disease such as emphysema are not easily interpreted. Peripheral neuropathy with decreased nerve conduction velocities has been measured at cross-sectional survey of employees of a Swedish copper smelter with an estimated average exposure to arsenic of 310 $\mu\text{g}/\text{m}^3$ for 28 years (Lagerkvist and Zetterlund, 1994). Encephalopathy may occur at higher, unquantified exposures. Vasospastic symptoms and Raynaud's phenomenon have been described among employees of the same smelter exposed to a time-weighted average of 360 $\mu\text{g}/\text{m}^3$.years for a mean of 23 years (Lagerkvist *et al.*, 1986 and 1988). In both Swedish studies the lowest estimated intensity of exposure to arsenic was 50 $\mu\text{g}/\text{m}^3$. Mild hypertension has been attributed to unquantified occupational arsenic exposures in a small Danish series (Jensen and Hansen, 1998). Dermatitis, including hyperpigmentation and hyperkeratosis has been described in two workforces; in one the estimated lowest observed adverse effects level (LOAEL) was 80 $\mu\text{g}/\text{m}^3$ (Perry *et al.*, 1948), but in the other the NOAEL was ten-fold lower (Mohamed, 1998).

2.3.3 Genotoxic and carcinogenic effects

2.3.3.1 Animals

81. There is extensive evidence that oral exposure of animals to arsenic leads to major chromosomal damage. There are no studies which address cancer development in animals after inhalation exposure to inorganic arsenic. However, intratracheal instillation studies in hamsters have provided evidence that both arsenite and arsenate can increase the incidence of lung adenomas and carcinomas. Although several

mechanisms of action have been proposed to explain the carcinogenicity of arsenic, at present there is no hypothesis that has received widespread support or that integrates the various clinical observations and the experimental data (Clewell *et al.*, 1999).

82. The primary hypotheses explaining the genotoxic and carcinogenic effects of arsenic include its inhibition of DNA repair enzymes, its ability to induce DNA amplification, especially oncogene amplification (perhaps by interfering with DNA repair and/or by inhibiting DNA synthesis) and its ability to cause hypomethylation of DNA by competing for methyl groups (Rudel *et al.*, 1996). However, hypermethylation may also occur with arsenic exposure. Hypermethylation of DNA, particularly in the promoter region, can result in inactivation of tumour suppressor genes or genes involved in DNA repair. Since these hypotheses involve types of damage that arsenic has been shown to induce with a sublinear response, they are consistent with the conclusion, drawn by some, that the dose–response relationship of arsenic-induced carcinogenicity is probably sublinear.
83. Some toxicologists believe that arsenic does not act by direct reaction with DNA but rather by interfering with DNA synthesis. Inhibition of DNA replicative mechanisms and effects on repair mechanisms could explain the chromosomal effects of arsenic and synergism with DNA-reactive chemicals. Other mechanisms for the carcinogenicity of arsenic have, on the basis of experimental evidence, been suggested; they include clastogenicity (chromosomal breakage) and mutagenicity (changes in the structure of genetic material). No single hypothesis has attracted universal support.
84. Recent studies have also suggested that DMA, a major metabolite of ingested inorganic arsenic in mammals, may initiate carcinogenesis in a number of organs (Yamanaka *et al.*, 2004; Wanibuchi *et al.*, 2004). The methylation of trivalent arsenic has been associated with DNA damage and activation of AP-1 dependent gene transcription (Styblo *et al.*, 2002). However, it is unclear if these metabolites are present in sufficient quantities or length of time to induce toxicity (Schoen *et al.*, 2004).

2.3.3.2 Humans

85. Human genotoxic effects, manifest as an increase in risk of chromosomal abnormalities in peripheral leucocytes, have been reported from one population, employed in a Swedish copper smelter. No associated exposure estimates were presented (Beckman *et al.*, 1977) and it not clear that the effects were attributable to arsenic exposure. Trivalent arsenic may be more genotoxic to human lymphocytes than pentavalent arsenic (Nordenson *et al.*, 1981).
86. Close attention has been paid to the carcinogenic effects of inhaled arsenic in the workplace; and in particular to the risk of lung cancer. This in part may reflect the relative ease with which secondary (mortality) data can be collected. Workers exposed to arsenic may also be exposed to other carcinogens such as tobacco smoking or other workplace toxins.

These need to be accounted for although this is commonly not the case in published studies.

87. There is some information suggesting that those who lived in the vicinity of smelters had an increased risk of lung cancer (Pershagen, 1985). When taken together with the studies of developmental defects mentioned below, these indicate a need to control non-occupational airborne exposures but the available data on exposure levels would not be helpful in standard setting.
88. Increased risks of lung cancer attributed to arsenic have been reported in serial studies of the workforces of two US and one Swedish smelters (Enterline *et al.*, 1995; Lee-Feldstein, 1986; Jarup *et al.*, 1989); and in a case-referent study of employees in a Chilean copper mine and smelter (Ferrecio *et al.*, 1995). In each of the serial cohort studies there have been increasingly careful attempts made to estimate airborne exposures but limited adjustment for smoking and none for other important occupational dust exposures. The lowest levels of cumulative exposure to inorganic arsenic that have been associated in these cohorts with statistically significant increases in lung cancer risk range from less than 250 to 2000 $\mu\text{g}/\text{m}^3$ years. An increased risk of lung cancer in the Chilean workforce was found only for those working in the smelter (average arsenic exposure 202 $\mu\text{g}/\text{m}^3$). The only recent data from the UK refer to the male employees of a tin smelter; since they were likely exposed to a variety of carcinogens it is not clear that their increased rate of death from lung cancer can be attributed to arsenic exposure alone (Binkes *et al.*, 2005).
89. It is likely that there are interactions between smoking and arsenic inhalation in the development of lung cancer, but the extent of this interaction may vary with the level of arsenic exposure (Hertz-Picciotto and Smith, 1993).
90. Associations between occupational arsenic exposures and other human cancers have been reported but the evidence for a causal relationship in each case is very weak.
91. The International Programme on Chemical Safety reviewed a large number of studies of the effects of long-term exposure to arsenic in drinking water. They concluded that arsenic in drinking water is causally related to increased risk of cancer in the skin, lungs, bladder and kidney, and to skin changes especially hyperkeratosis and changes in pigmentation (IPCS, 2001). Exposure–response relationships and high risks had been observed for each of these end-points. Many of the studies had been undertaken in Taiwan, but similar results have been reported in studies undertaken in Bangladesh and South America. Increased risks of lung and bladder cancer and of arsenic-associated skin lesions have been reported to be associated with ingestion of drinking-water at concentrations ≤ 50 μg arsenic/litre. For an adult consuming 2 litres of water per day, this equates to a daily intake of ≤ 100 μg .

2.3.4 Reproductive and developmental toxicity

92. Adverse reproductive and developmental effects have been studied, by a single research group, among the female workforce of a Swedish copper smelter. Small increases in the risks of low birth weight (Nordström *et al.*, 1978), spontaneous abortion (Nordström *et al.*, 1979a) and congenital malformation (Nordström *et al.*, 1979b) have been reported. These have not been associated with direct estimates of arsenic exposure and the effects of confounding exposures cannot be ruled out. Increased risks of similar outcomes have been described in the population living close to the same smelter; there are no useful exposure data for this population. A small case-control study in a population living in central Texas, suggested an increased risk of stillbirth in Hispanic women estimated to have had high exposure to arsenic from living near a pesticides factory (Ihrig *et al.*, 1998). Exposure estimates were based on current home address; 'high' exposures were those estimated to be greater than 100 ng/m³. However, no effect was found in children of non-Hispanic mothers.

2.4 Evaluations and recommendations by other organisations

93. Guidelines and limits on exposure to arsenic in ambient air have been published by the WHO, the EC, Defra and the Environment Agency (EA). The US Environmental Protection Agency (EPA) and the US Agency for Toxic Substances and Disease Registry (ATSDR) have considered arsenic but not published guidelines. The UK HSE and the American Conference of Governmental Industrial Hygienists (ACGIH) have published limits and guidelines on workplace exposures.
94. The WHO (2000) classify arsenic compounds as human carcinogens by inhalation exposure. The unit risk for lung cancer is 1.5×10^{-3} per $\mu\text{g}/\text{m}^3$ in air based on the results of studies of three cohorts of smelter workers (WHO, 2000). Concentrations of 66 ng/m³, 6.6 ng/m³ or 0.66 ng/m³ equate respectively to excess lifetime risks of 1 in 10,000, 1 in 100,000 and 1 in 1,000,000.
95. The US EPA has estimated that the lifetime lung cancer risk from exposure to airborne arsenic is 4.3 in 1000 for every increase in exposure by 1 $\mu\text{g}/\text{m}^3$. Concentrations of 20 ng/m³, 2 ng/m³ and 0.2 ng/m³ are predicted to increase life-time cancer risks of 1:10 000, 1:100 000 and 1:1000 000, respectively (US EPA, 1984).
96. The EC Position Paper (2000) and CSTEE (2001) proposed a limit value for arsenic for non-cancer effects of 100 ng/m³. The limit value for cancer effects proposed by the EC was 4–13 ng/m³. Following discussion of the genotoxicity of arsenic, however, the European Environment Bureau (EEB) has proposed a value of 3 ng/m³ as a suitable future revision of the limit. Industry argued that a limit value of 50 ng/m³ would provide sufficient protection. The target value for arsenic, "to be attained as far as possible", in the Fourth Daughter Directive on Ambient Air Quality is 6 ng/m³ and is effective from 31 December 2012 (Directive 2004/107/EC).

97. Defra and the EA (2002) proposed an index dose for arsenic for the purposes of deriving Soil Guideline Value for contaminated land. The Index Dose represents a dose that poses a minimal risk level from possible airborne exposure to arsenic, with the additional requirement that exposure should be as low as reasonably practicable (ALARP). There was clear evidence of carcinogenic and genotoxic potential for inorganic arsenic with no threshold for effect. The index dose was based on the concentration believed to be associated with a 1 in 100,000 excess lifetime lung cancer risk (6.6 ng/m³, WHO, 2000). Assuming a 70 kg adult inhales 20 m³ air per day, the index dose was calculated to be 0.002 µg/kg body weight/day.
98. The Health and Safety Commission has set a workplace exposure limit, time-weighted over 8 hours, of 100 µg/m³ for arsenic and its inorganic compounds (HSE, 2005). The concentration was considered to be well below that level at which a raised incidence of respiratory tract cancer had been observed and below the NOAEL for respiratory tract irritation.
99. The ACGIH Threshold Limit Value (TLV) for inorganic arsenic, a concentration to which nearly all workers may be repeatedly exposed over a working lifetime without adverse effects, is 10 µg/m³ (8 hour average).

2.5 Justification for air quality guideline

100. Air quality guidelines for four different adverse human health endpoints might be considered for acute respiratory irritation, chronic, non-malignant disease adverse reproductive effects and cancer.
101. Workplace measurements suggest that acute irritant effects are unlikely at short-term exposures of less than 100 µg/m³. There are workplace exposure data, albeit scanty, for several chronic non-malignant adverse health endpoints: peripheral neuropathy and Raynaud's phenomenon. The lowest exposure at which any of these has been reliably reported is 50 µg/m³.
102. Adverse reproductive effects have been reported in a very small number of studies. In none can the effects of confounding exposures be ruled out. Only one study – of stillbirths – provides an estimate of (current) exposure to arsenic; this is reported to be greater than 100 ng/m³.
103. There is sufficient evidence to classify arsenic as a human carcinogen. The most important effect for inhaled arsenic appears to be the induction of lung cancer. There are insufficient human data on issues such as genotoxicity to know whether or not there is a threshold of exposure and whether or not the relationship between dose and risk (especially at low exposures) is linear or otherwise.
104. The approach adopted here for standard-setting is directly analogous to that used by EPAQS in setting standards for other chemical carcinogens such as benzene and polycyclic aromatic hydrocarbons. It uses data from studies of occupationally exposed workforces in three non-UK smelters. The Panel considered the data from these studies to be of equal validity. The lowest range of cumulative exposure that was

associated with a statistically significant increase in lung cancer risk was less than $250 \mu\text{g}/\text{m}^3 \cdot \text{years}$ in a Swedish workforce and less than $833 \mu\text{g}/\text{m}^3 \cdot \text{years}$ and $750\text{-}2000 \mu\text{g}/\text{m}^3 \cdot \text{years}$ in two US workforces. The Panel considered it appropriate to take the lowest of these in order to provide maximum protection of the public from ambient exposures.

105. The mid-point of the exposure range from the Swedish study is $125 \mu\text{g}/\text{m}^3 \cdot \text{years}$ which converts to an average concentration of $3 \mu\text{g}/\text{m}^3$ over a 40 year working lifetime. If this concentration is considered as a LOAEL then, following the precedent set in our report on polycyclic aromatic hydrocarbons, division by a factor of 10 giving a concentration of $0.3 \mu\text{g}/\text{m}^3$ ($300 \text{ ng}/\text{m}^3$) provides a notional NOAEL. This has further been divided by a factor of 10 to allow for the greater exposure duration of the general public and a further factor of 10 to allow for the presence of susceptible groups from within the general population. This leads to a recommended guideline value of $3 \text{ ng}/\text{m}^3$.
106. The sensitivity of the proposed guideline value was examined by comparing it with alternative approaches. One of these was based on the concept of unit risk, which is the risk of outcome associated with a lifetime exposure to $1 \text{ ug}/\text{m}^3$. This is estimated from relative risks obtained from epidemiological studies and is justified if it is believed, as in the case of genotoxic agents, that there is no threshold and that there is a linear exposure-response relationship. Essentially, it is an extrapolation beyond the data to very low concentrations. This makes it subject to assumptions about the shape of the exposure response curve. This approach is used by the WHO and other authorities for carcinogenic compounds. The WHO estimated a unit risk of 1.5×10^{-3} per $\mu\text{g}/\text{m}^3$, based on data from three copper smelters. A concentration of $1 \text{ ng}/\text{m}^3$ would be associated with an excess life-time risk of 1.5 in a million. This level is close to that of $3 \text{ ng}/\text{m}^3$ proposed by EPAQS using a different method. Thus, it appears that the derived guideline is robust to the method of derivation.

2.6 Recommendation

$3 \text{ ng}/\text{m}^3$ total inorganic arsenic in the PM_{10} size fraction, as an annual mean.

107. **The Panel proposes that a maximum level of $3 \text{ ng}/\text{m}^3$ should offer a high level of protection against the risk of lung cancer and other health effects. For this, as other carcinogens, the Panel advocates a progressive reduction in airborne concentrations below this guideline.**

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Chapter 3

Nickel

3.1 Background

3.1.1 Basic chemical information

108. Nickel is a silvery white lustrous, hard metal, one of a group of elements known as transition metals. It shares magnetic properties with iron and cobalt and is the basis of several alloys, the most important of which is stainless steel. Nickel metal is also used in its own right in items such as jewellery and watch casings and as a plating agent to give a bright corrosion-free finish. It also finds use in welding rods, coinage, batteries and chemical catalysts. It occurs naturally in the environment in air water and soil. The principal commercial ores are the sulphide and oxide/silicate.
109. Nickel can exist in several oxidation (valence) states, but the divalent form is virtually ubiquitous in the environment. Salts can be water soluble (nitrate, sulphate, chloride) or insoluble (oxides, sulphides). Nickel salts and metal readily form complexes with the amino acid histidine, both free and when combined into protein and this factor probably accounts for the tendency to provoke hypersensitive (allergic) reactions in some individuals.
110. Nickel is established as an essential trace element in animals, deficiency may affect reproduction (Yokoi *et al.*, 2003) but this has not been demonstrated in man, probably because the universal occurrence in food precludes deficiency symptoms (WHO, 2000).
111. There are no data on the chemical forms of nickel from natural sources in the atmosphere (WHO, 1991). If likely sources are considered then part of airborne nickel may exist as pentlandite ((FeNi)₉S₈) and garnierite (a silicate mixture) (Schmidt and Andren, 1980). The chemical composition of nickel compounds released from man-made sources differs from that from natural sources because of the different processes involved. Studies by Hansen and Fisher (1980) and Hansen *et al.* (1984) indicated that most of the nickel present in fly ash particles (from coal combustion), was soluble and associated primarily with sulphate. Thus, nickel emissions to atmosphere from coal and oil combustion are likely to be composed mainly of (soluble) nickel sulphate, with smaller amounts of nickel oxide and nickel combined with other metals in complex oxides. Alterations in the chemical forms, following distribution in the atmosphere, have not been investigated.
112. The distribution of nickel among suspended particulates in air will determine the fraction that is inhalable. Data on the size distribution of nickel particulates are limited. Lee and von Lehmden (1973) reported

mass median diameters of nickel particulates in urban air in the range of 0.83-1.67 μm , 28-55% of the particles being $<1 \mu\text{m}$. A more recent summary of size distribution of trace elements in different areas yielded a (similar) mass median diameter for nickel particulates of 0.98 μm (Milford and Davidson, 1985). Nickel was found to be most concentrated in the smallest particles emitted from coal-fired power plants (Natusch *et al.*, 1974). Particles of mass median diameter 0.65-1.1 μm contained 1600 mg nickel/kg while 4.7-11 μm particles contained about 400 mg nickel/kg.

3.1.2 Sources of nickel in the UK atmosphere

113. The main source of nickel emissions to the air in the UK has been the combustion of oil-based fuels in power stations, refineries, industry and for domestic heating (Dore *et al.*, 2005). The main sources reported in the UK National Atmospheric Emissions Inventory for 2004 include emissions from refineries, industry, shipping and non-road mobile machinery. Combustion of fuel oil at refineries, in industry and for shipping contributed 66% of the national total in 2004. Combustion of petroleum coke at refineries contributed 17% and combustion of gas oil for shipping and non-road mobile machinery contributed 7%. Emission from metal industry sources make up a relatively small percentage of total UK emissions (4%) but may constitute the most important source in the vicinity of specific industrial plant.
114. Nickel is emitted in many different forms. Approximately 55% of UK emissions in 2004 were estimated to be soluble nickel salts such as sulphates and chlorides and this constituted the highest percentage for most combustion emission sources (combustion sources are assumed to emit 58% as soluble nickel salts, 39% as nickel oxides, 3% as nickel sulphides and 0.5% as nickel carbonyl). Approximately 40% of emissions were estimated to be as nickel oxides, including the majority of emissions from metal industry processes (100% from the iron and steel industry and 50% of the emissions from non-ferrous metal industries, the remaining 50% is assumed to be metallic nickel). Emission of nickel sulphides contributed about 3%, metallic nickel about 1.5% and emissions of nickel carbonyl contributed only 0.5%. The speciation of emissions is subject to considerable uncertainty.
115. UK emissions of nickel are estimated to have declined by 82% between 1970 and 2004 as a result of reductions in the combustion of oil in power stations, industry and for domestic heating.

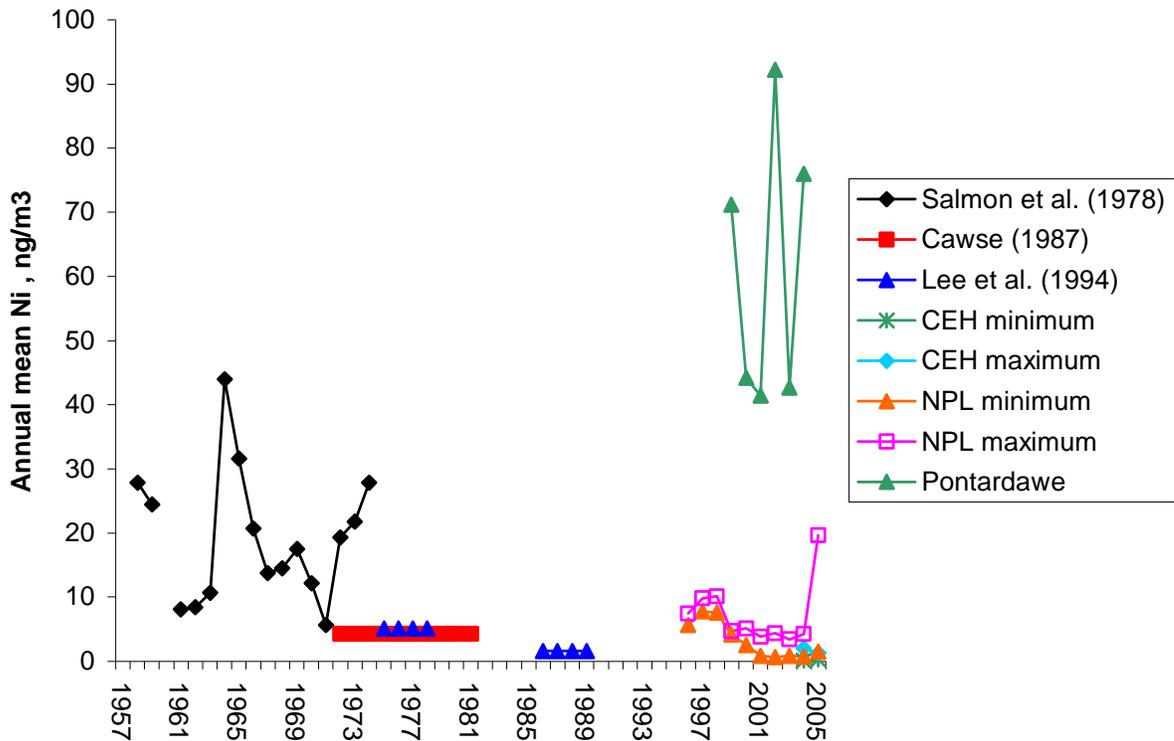
3.1.3 Ambient concentrations

116. Measured annual mean nickel concentrations in air in 2005 ranged from 0.3 to 1.5 ng/m^3 at rural locations, 1.9 to 4.5 ng/m^3 at urban locations and 2.3 to 19.6 ng/m^3 at monitoring sites close to metal industries. An annual mean concentration of 76 ng/m^3 was measured at a local authority-operated site south Wales in 2004 (Neath Port Talbot County Borough

Council, 2006). Concentrations at rural monitoring sites have declined by about 80% between 1972 and 2001, reflecting the changes in UK emissions.

117. Figure 3.1 presents the time history of the available rural measurements of total particulate nickel from 1957 through to 2005. Annual mean levels fell from their maximum levels in the early 1960s to their current minimum levels. For recent years the figure shows the range of values measured at monitoring sites in the national networks. The highest measured concentrations in recent years in urban or industrial areas are generally similar to or lower than the historical rural concentrations. Current rural levels appear to be about a factor of 20 below their historical levels. The concentrations measured at the local authority monitoring site close to an industrial plant at Pontardawe in South Wales are considerably higher than at other monitoring sites.

Figure 3.1: Time history of the available annual mean total particulate nickel concentrations in rural air from 1957 through to 1989 for Harwell, Oxfordshire (Cawse, 1987; Lee *et al.*, 1994; Salmon *et al.*, 1978), the maximum and minimum values measured in the national monitoring networks from 2000 to 2005 (NPL, 2006; CEH, 2006) and concentrations of airborne nickel monitored at Pontardawe (Neath Port Talbot County Borough Council, 2006).



3.1.4 Human Exposures

118. The major non-occupational source of human exposure to nickel is via food with further contributions from drinking water and air. Cigarette smoke also contains significant quantities of nickel. Release to atmosphere from natural sources (mainly windblown dust, volcanoes and vegetation) has been estimated (Duce *et al.*, 1991; Giusti *et al.*, 1993) at 30,000 tonnes (as nickel) annually, with about 1.5 times that quantity coming from anthropogenic sources.
119. Food from all sources contains trace quantities of nickel. Levels in most foods are similar and generally below 1 ppm (1 mg/kg) but nuts and cocoa may have significantly higher levels (IARC, 1990). Daily exposure from the diet has been estimated to range from about 70 – 160 µg for both USA and European diets (ATSDR, 2003), with typical daily exposures from drinking water and air of 8 and 0.4 µg, respectively. The WHO (1991) reported higher values, with 200 - 300 µg/ day considered as the range of mean oral intakes for a Western adult. Exposures from all sources may increase in areas close to significant sources of the metal such as refineries. In Sudbury, Ontario, mean daily exposure from drinking water and air was reported to average 140 and 15 µg respectively. Mainstream cigarette smoke contains 0.04 - 0.58 µg/cigarette (WHO, 2000): assuming 50% absorption a smoker consuming 20 cigarettes/day will increase his/her airborne exposure by up to 6 µg, or about 15 times the ambient value. Other potential sources of non-occupational nickel exposure are from watches and jewellery in contact with the skin, (negligible quantities are absorbed by this route but the exposures can be important for those sensitised to the metal) and from leaching and corrosion of nickel in prosthetic devices.
120. Occupational exposures to nickel are highest for those involved in production (mining and refining) processing and use, but a wide range of trades are exposed to a lesser extent from using/repairing components or devices containing nickel or its alloys, especially stainless steel. In all cases the inhalation route seems dominant when considering health effects, with dermal exposures important for those individuals with hypersensitivity: Oral exposures are of less significance, even though this route is quantitatively dominant.
121. In mining and refining historical exposures have been very high with values of up to 100 mg/m³ recorded. These are exceptional: a more realistic estimate of historical exposures is in the region of 1-5 mg/m³. The chemical form of nickel present in workplace atmospheres is not always easy to determine, but generally the highest exposures have been to the less soluble compounds. These may be retained in the lung for long periods resulting in significant increased total body burden. The normal body burden of nickel approximates 0.1 µg/g in non-occupationally exposed individuals, with much of this in the lung. Svenes and Andersen

(1998) reported that the nickel content of lung tissue taken from a group of ex- nickel refinery workers was $50 \pm 150 \mu\text{g/g}$ (dry weight), compared with $0.74 \pm 0.44 \mu\text{g/g}$ in a similar group unconnected with the industry.

122. There have been no specific studies to determine whether children are more susceptible than adults to the effects of nickel. Limited evidence of an increased susceptibility from dermal exposures is considered more likely to reflect potential for exposure (via body piercing) than increased sensitivity (ATSDR, 2003).

3.2 Absorption and Excretion

3.2.1 Pulmonary Absorption

123. The measured particle size for atmospheric nickel indicates that most of the inhaled particles will deposit in the lung (WHO, 2000) with up to 40% being retained in the deep lung where clearance is more prolonged. There are marked differences in the solubility of nickel compounds. In general, nickel chloride and nickel sulphate are soluble while nickel oxide and nickel subsulphide are insoluble. Soluble nickel compounds are rapidly removed from the lung (Carvalho and Ziemer, 1982). Menzel *et al.* (1987) demonstrated a saturable clearance mechanism for soluble nickel compounds from rat lungs, calculating a maximum clearance velocity of 34.6 ng/g of lung tissue per hour for nickel chloride. In contrast approximately 50% of a dose of nickel oxide, which is much less soluble, was still present in the lungs of golden hamsters after 45 days. Moreover, only 10% nickel sulphide, which is of intermediate solubility, is retained after 35 days (Valentine and Fisher, 1984).

3.2.2 Metabolism

124. The biological half-life of nickel depends on the compound tested and thus its solubility as discussed above. Once in blood, nickel binds to the blood proteins, albumin and α -2-macroglobulin. The bound nickel can exchange with free histidine, leading to a pool of low molecular weight nickel-L-histidine complexes, which can cross biological membranes. Tissue based metabolism of nickel has been extensively studied in animals and has been shown to involve oxidation/reduction (redox) reactions generating the trivalent form, nickel (Ni^{3+}). The extent of redox cycling within different tissues is likely to be influenced by the availability of other oxidising and reducing species.

3.2.3 Tissue distribution and excretion

125. Most soluble forms of inhaled nickel are excreted in urine. Thus high levels of (insoluble) nickel oxide in air give relatively low plasma and urine concentrations but high levels in the nasal mucosa and presumably the lung (Torjussen and Anderson, 1979; Høgetveit *et al.*, 1978). As nickel-

induced cancer of the lung is a major cause for concern, nickel absorbed into the blood could be considered of less significance than that retained in the lung, although local effects may be mediated by soluble forms.

3.3 Health Effects/Toxicology

3.3.1 Acute and chronic effects

126. Studies in animals have shown that chronic inflammation of the lung and/or nasal passages follows repeated dose inhalation of a wide range of nickel compounds. The effects seen are qualitatively similar in both rats and mice. However, the no observed adverse effects level (NOAEL) established in the various reported studies shows wide variation, which in part reflects the solubility of the compound tested: more soluble compounds show NOAEL about an order of magnitude lower than the insoluble salts. The results of several studies have been summarised by ASTDR (2003). In a 13 week study, nickel sulphate induced an inflammatory response in the lungs of female rats with a NOAEL of 0.06 mg/m³. However, in the chronic (two year) studies conducted by the USA National Toxicology programme (NTP, 1996 a,b,c) both rats and mice showed limited signs of respiratory irritation/inflammation at 0.03 mg/m³ (the lowest dose tested), although the effect was equivocal and confined to the few rats examined at interim sacrifice (NTP, 1996b).
127. Apart from nickel sensitivity, which is common in the general population, non cancer effects in humans have been reported only in workers involved in the production or intensive use of nickel containing substances. Exposure to nickel by inhalation causes adverse effects, including lung irritation, and pneumonia. At very high concentrations, acute inhalation has been reported to cause severe pulmonary irritation. A worker exposed to an estimated 382 mg/m³ of metallic nickel died from adult respiratory distress syndrome. Acute inhalation effects of nickel carbonyl fall into two categories, immediate and delayed (Defra and EA, 2002a; IEH, 2003). The immediate response includes headache, nausea, dizziness, vomiting, insomnia and irritability. In mild cases this resolves within a day, with more severe exposures, typically in excess of 50 mg/m³, symptoms such as chest pain, dyspnoea (shortage of breath) and oedema (fluid in the lung) can occur 12-120 hours after exposure (EC, 2000; WHO, 1991). Severe lung damage may occur at high concentrations, but non-occupational exposure to nickel carbonyl is unlikely.
128. Evidence linking chronic exposure to non-cancer mortality has been mixed and difficult to interpret due to co-exposures to other substances (ATSDR, 2003). Chronic exposure has been linked to irritation and damage to the upper and lower respiratory tract manifest as septal damage, chronic sinusitis, chronic bronchitis, reduced ventilatory capacity and pulmonary fibrosis (Kilburn *et al.*, 1990; Berge and Skyberg, 2003). Occupational exposure has been associated with asthma in a few reports; this is thought

to be caused by either primary irritation of the airways or an allergic response. Nickel sensitisation may occur by inhalation, as well as by oral or dermal routes, at least after occupational exposures. Once sensitised, contact with a small amount of nickel is sufficient to cause dermatitis. The mechanism is believed to relate to both allergy and irritation. Occupational exposure has not been associated with other health outcomes, apart from some renal and immunological abnormalities of uncertain clinical significance.

129. In a recent paper Lippmann *et al.* (2006) showed that mice, specially bred to be susceptible to atherosclerosis when fed a high fat diet, were exposed to collected airborne particulates there were significant reductions in heart rate which correlated with the nickel content of the particulate. Significant changes were associated with 14 days when peak nickel concentrations in the particulate (approximately 175 ng/m³) were seen compared to the average value of 43 ng/m³. In a previous investigation in rats Campen *et al.* (2001) reported that inhalation of nickel aerosol for six hours/day for four days caused delayed effects including slowed and irregular heart beat and reduced body temperature at concentrations > 1.2 mg/m³. In contrast, no significant effect on heart rate was reported in beagle dogs following three hours inhalation exposure on three successive data to a nickel sulphate aerosol at a concentration of 0.05 mg/m³ (Muggenburg *et al.*, 2003). In a study of boilermakers, Magari *et al.* (2002) found evidence of an association between exposure to transition metals and heart rate variability, although the specific effect associated with nickel was small and not statistically significant.

3.3.1.1 Hypersensitivity

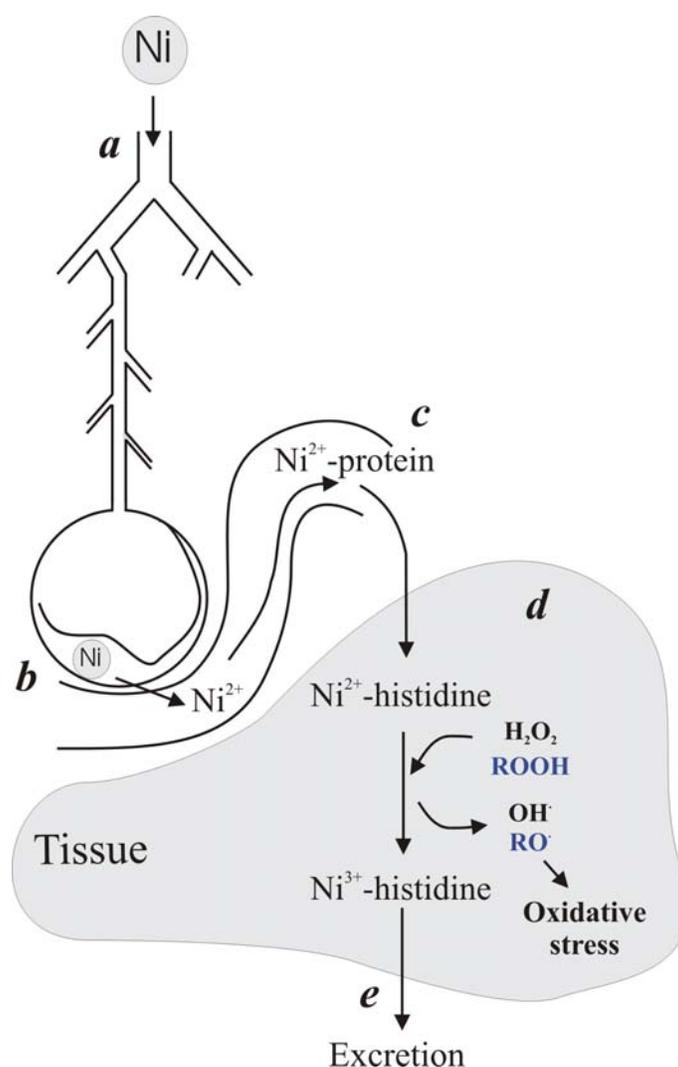
130. Nickel and its soluble salts are potent skin sensitisers with allergic skin reactions being the most common health effect (HSE, 1997; WHO, 1991). Skin sensitisation to nickel, identified by patch testing or clinical history, affects 10-20% of the population with a higher prevalence in women which is thought to reflect an increased exposure to nickel in jewellery. Important risk factors are skin contact with jewellery, skin piercing and handling of coins and other nickel-containing products. Rare cases of asthmatic lung disease have been reported after occupational exposure to inorganic nickel compounds (WHO, 1991) but there is no evidence that airborne nickel causes allergic reactions in the general population.

3.3.1.2 Mechanism(s) of acute toxicity

131. Although nickel compounds cause the oxidation of lipids (Stinson *et al.*, 1992; Athar *et al.*, 1987), proteins (Zhuang *et al.*, 1994) and nucleic acids (Stinson *et al.*, 1992, Lynn *et al.*, 1997), intracellular radical production (Huang *et al.*, 1994a,b), as well as intra-cellular glutathione depletion (Rodriguez *et al.*, 1991; Herrero *et al.*, 1993; Li *et al.*, 1993) there is little

evidence that free nickel undergoes redox cycling reactions, in contrast to metals such as iron, copper, chromium, vanadium and cobalt. Hydrated Ni^{2+} ions react slowly with hydrogen peroxide to form hydroxyl radicals and are not efficient catalysts of peroxide decomposition. Their activity in models where lipid, protein and DNA oxidation have been observed reflects the binding of nickel to biological ligands such as the imidazole nitrogen of histidine that reduces its oxidation potential allowing it to be oxidised to Ni^{3+} by strong oxidants, such as hydrogen peroxide and organic hydroperoxides (Datta *et al.*, 1992). This ligand-dependent $\text{Ni}^{2+}/\text{Ni}^{3+}$ redox cycling of nickel results in the formation of oxygen radicals via Fenton-type reactions (Klein *et al.*, 1991; Lin *et al.*, 1992). Consistent with this view, studies have shown that the formation of alkyl, alkoxy and peroxy radicals by nickel and cumene hydroperoxide occurs only in the presence of glutathione, carnosine, homocarnosine or anserine (Shi *et al.*, 1992). This ligand-dependent reaction may also occur with histones: these nuclear protein- Ni^{2+} complexes permit hydroxyl radical generation in the presence of hydrogen peroxide resulting in extensive DNA base modification (Nackerdien *et al.*, 1991). The above reactions, which are summarised schematically in Figure 3.2, are associated with soluble nickel salts and may be important in the induction of an inflammatory response. Further evidence suggests that insoluble particulate nickel compounds, including the sulphide and subsulphide, can also induce the release of reactive oxygen species from phagocytic cells (Costa and Mollenhauer, 1980). These insoluble forms of nickel have been shown to be more carcinogenic than soluble nickel and *in vitro* studies have demonstrated that they induce greater intracellular free radical production than soluble nickel salts (Huang *et al.*, 1994a,b).

Figure 3.2: Nickel - Pulmonary absorption, metabolism, tissue distribution and excretion. (a) Inhaled particles containing nickel deposit along the length of the respiratory tract. (b) The most soluble nickel compounds are absorbed into blood to the greatest extent and thus higher proportions of low soluble nickel compounds remain for much longer in the lung. (c) In blood, nickel is transported attached to serum proteins such as albumin and α -2-macroglobulin. (d) In tissues, nickel binds to biological ligands such as the imidazole nitrogen of histidine. This decreases its oxidation potential allowing it to be oxidized to Ni^{3+} by strong oxidants, such as hydrogen peroxide and organic hydroperoxides. This ligand-dependent $\text{Ni}^{2+}/\text{Ni}^{3+}$ redox cycling of nickel results in the formation of oxygen radicals, which in turn oxidise cellular targets such as lipids, proteins and DNA. (e) urinary excretion is the main route of clearance although small amounts are lost in sweat and saliva. As soluble forms of nickel enter the blood in high amounts, urinary excretion rates for these compounds are higher than for low-solubility nickel compounds.



3.3.2 Genotoxicity

132. The results of bacterial mutation tests *in vitro* are equivocal. This probably reflects variations in sensitivities of tester strains used and the test conditions (ASTDR, 2003). The results from sister chromatid exchange studies in mammalian cells and cultured human lymphocytes are positive, as are those for cellular transformation. In the latter studies, the extent of induction of cellular transformation was shown to depend on the cellular uptake of the particular test compound (Costa, 1989).
133. Most of the studies *in vivo* were negative, but one study with oral dosing and a second by injection, showed increased incidence of micronuclei in mice after dosing with soluble nickel compounds. One study with two groups of nickel refinery workers (Waksvik and Boysen, 1982) showed a slight but significant increase in chromosome aberrations (but not breaks or sister chromatid exchanges).
134. These observations led the Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE) to conclude that a genotoxic mode of action could not be discounted (CSTEE, 2001). There is evidence that genotoxic effects of nickel compounds may be indirect, through inhibition of DNA repair systems (Hartwig, 1998). This possibly reflects the ability of nickel to form complexes with the amino acid histidine which may then take part in redox reactions (see above).

3.3.3 Carcinogenicity

3.3.3.1 Animal studies

135. No experimental evidence has been found to show that nickel compounds are carcinogenic when administered orally or cutaneously.
136. Ottolenghi *et al.* (1974) reported a significant increase in lung tumour incidence in rats following nickel subsulphide inhalation exposure for two years. The USA National Toxicity Program (NTP, 1996a,b,c) examined the carcinogenicity of nickel sulphate hexahydrate, nickel oxide and nickel subsulphide in rats and mice. None of the compounds tested induced tumours in mice. Nickel sulphate induced no tumours in rats, but increased numbers of both benign and malignant tumours (adenomas and carcinomas) were found in rats exposed to either the oxide or subsulphide.

3.3.3.2 Human studies

137. Studies of occupationally-exposed populations have consistently, and with clear evidence of an exposure-response relationship, found increased risks of nasal and lung cancers in workers exposed to airborne nickel compounds (Seilkop and Oller, 2003). These cancers are not histologically specific. The relative risks are higher for nasal cancers.

138. Those exposed to high concentrations of nickel compounds at work are often also exposed to other carcinogens such as arsenic; thus associations between cancer and nickel exposure are likely to be confounded. Where there is such confounding, guideline values extrapolated from occupational risk estimates are likely to be conservative.
139. The highest risks are found among those working in nickel smelting, refining or sintering (Muir *et al.*, 1994). No significant risks have been reported among nickel electroplaters or those engaged in nickel alloy manufacture (Sorahan, 2004). Metallic nickel is believed not to be carcinogenic.
140. There is uncertainty over the relative human carcinogenicity of the various nickel compounds. The contention that risk was related chiefly to exposures to insoluble compounds (nickel oxides or sulphides) has been tempered by recent epidemiological evidence that points also to a risk from exposure to soluble compounds, particularly nickel sulphate (Anttila *et al.*, 1998; Grimsrud *et al.*, 2002).
141. The effects of cigarette smoking and nickel compound exposure appear to be additive (Magnus *et al.*, 1982)
142. Evidence concerning cancers in other sites is far less conclusive. In 1990 the International Committee on Nickel Carcinogenesis in Man concluded that there was no risk from airborne nickel compounds for non-nasal/lung cancers (International Committee on Nickel Carcinogenesis in Man, 1990); more recent studies however have suggested that there may be increased risks of stomach (Anttila *et al.*, 1998; Pang *et al.*, 1996) and pancreatic cancer (Ojajarvi *et al.*, 2000).

3.3.4 Reproductive and developmental toxicity

143. Several animal studies (reviewed by Defra and EA, 2002a) have shown that soluble nickel salts may induce testicular damage, leading to reduced fertility, and developmental toxicity in rats and mice. Inhalation exposures of six hours/ day for 12 days to nickel sulphate (1.8 mg/m^3) or nickel subsulphide (1.6 mg/m^3) produced testicular degeneration in rats and mice (ACGIH, 1996).
144. Hamsters and rats exposed to nickel carbonyl (0.16 mg/m^3 or higher) during gestation showed foetal mortality and foetal malformations.
145. A single intraperitoneal injection of nickel chloride at 20 mg/kg body weight to groups of female mice on days 1 to 6 of gestation, was associated with increased frequency of early and late foetal "resorptions" and of stillborn and abnormal foetuses (Storeng and Jonsen, 1981). The authors concluded that nickel chloride "may influence mouse embryos during the passage though the oviduct and on their subsequent development after implantation". Mas *et al* (1986) injected radioactive nickel chloride into pregnant rats, and showed that that nickel enters foetal tissue, although

- concentration in the foetus is lower than in the dam. Diwan *et al.* (1992) injected pregnant rats with Nickel (II) acetate at 90 µg/kg/body weight on days 16-18 of gestation. Offspring had an increased incidence of pituitary tumours - suggesting that "Ni (II) is a complete transplacental carcinogen for rat pituitary".
146. Casey and Robinson (1978) showed that nickel crosses the human placenta *in vivo*. Since measured levels were similar to those reported for adult liver, the Authors concluded that: i) nickel salts must cross the placenta readily and ii) the supply to the fetus depends on the nickel status of the mother. Chen and Lin (1998) incubated human placental explants with nickel chloride (1 to 5 mM, 12 hrs), and found a dose-dependent increase in permeability (indicated by potassium release) and lipid peroxidation. The authors speculated that these changes may cause "damage to the fetus" - but there are no direct data in support.
147. Women working in a Russian nickel refinery had a higher rate (about double) of spontaneous abortions and increased congenital malformations compared with women working in local construction industries. Exposures – primarily to nickel sulphate – were estimated to be between 80 and 200 µg/m³ (Chashschin *et al.*, 1994). It is not clear that these outcomes can be attributed to inhalation of nickel compound(s).

3.4 Evaluations and recommendations by other organisations

148. Guidelines and limits on exposure to nickel in ambient air have been published by the WHO, Defra and the EA, the European Commission (EU), CSTE, the US Environmental Protection Agency (EPA) and the US agency for Toxic Substances and Disease Registry (ATSDR).
149. The WHO (2000) classify nickel compounds as human carcinogens by inhalation exposure and derived an incremental unit risk of 3.8×10^{-4} per µg/m³ in air. Lifetime exposure to concentrations of 250 ng/m³, 25 ng/m³ and 2.5 ng/m³ are calculated to increase life-time cancer risks by not more than 1:10,000, 1:100,000 and 1:1,000 000, respectively.
150. The EC Working Group on Arsenic, Cadmium and Nickel compounds proposed an overall limit value for nickel for both carcinogenic and non-carcinogenic effects of 10-50 ng/m³ as an annual mean (EC, 2000). This value is calculated to limit the excess lifetime cancer risk to not more than one in a million. The CSTE suggested that a limit value of 20 ng/m³ would provide "reasonable protection for the general population to the carcinogenic effects of nickel compounds in ambient air" (CSTE, 2001). This limit value was adopted as a target value, "to be attained as far as possible", in the Fourth Daughter Directive on Ambient Air Quality and is effective from 31 December 2012 (Directive 2004/107/EC).
151. Defra and the EA (2002b) proposed an index dose for nickel to derive a Soil Guideline Value for contaminated land. The index dose is intended to

- pose a minimal risk from exposure, with the additional requirement that exposure should be as low as reasonably practicable (ALARP). The index dose for nickel was determined as 6 ng/kg body weight/day based on an airborne concentration of 20 ng/m³. For threshold effects, the tolerable daily intake from soil (by inhalation) was determined as 2 and 1 ng/kg body weight/day, respectively, for adults and six year old children.
152. The US EPA estimated the lifetime cancer risk from exposure to nickel refinery dust to be $2.4 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ from the results of four epidemiological studies (US EPA, 1991a). Concentrations of 400 ng/m³, 40 ng/m³ and 4 ng/m³ are calculated to increase life-time cancer risks by no more than 1:10 000, 1:100 000 and 1:1 000 000, respectively. The US EPA derived a further unit risk estimate of $4.8 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ for nickel subsulphide by applying a factor of two to account for the 50% (approximately) nickel subsulphide composition of refinery dust (US EPA, 1991b). Concentrations of 200 ng/m³, 20 ng/m³ and 2 ng/m³ are calculated to increase life-time cancer risks by no more than 1:10,000, 1:100,000 and 1:1,000,000, respectively.
 153. The ATSDR (2003) derived intermediate and chronic inhalation minimal risk levels (MRLs) of 200 ng/m³ and 90 ng/m³ for nickel sulphate hexahydrate on the basis of inflammation in rats. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without appreciable risk of adverse effects (other than cancer) over a specified duration of exposure (ATSDR, 2003).
 154. The UK HSE workplace exposure limits (WEL) for nickel and its inorganic compounds (except nickel tetracarbonyl) are 0.1 mg/m³ (as Ni) for water soluble compounds and 0.5 mg/m³ (as Ni) for insoluble compounds. The HSE considered the critical health effects resulting from nickel exposure to be cancer (nickel oxides and sulphides) and skin sensitisation (water soluble nickel compounds). A 'Skin' notation is also applied, based on sensitisation as one of the critical health effects.
 155. The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV), a concentration to which nearly all workers may be repeatedly exposed over a working lifetime without adverse effect, is 1.5 mg/m³ for elemental nickel, 0.1 mg/m³ for soluble inorganic compounds, 0.2 mg/m³ for insoluble compounds and 0.1 mg/m³ for nickel subsulphide (all as 8 hour averages).

3.5 Justification for air quality guideline

156. The major health effect from exposure to nickel compounds by inhalation is toxicity to the respiratory tract, including lung and nasal cancer, although the latter is probably confined to occupational exposures. The exact agent responsible for this effect remains controversial. Animal experiments have implicated insoluble salts, especially the subsulphide and the oxide, and these are certainly more potent carcinogens than the soluble salts. Nickel

- sulphate (soluble) did not increase lung cancer incidence in animals. However, more recent epidemiological studies have indicated that soluble nickel salts may contribute to the incidence of lung cancer in refinery workers (Grimsrud *et al.*, 2002). Sensitisation may result from inhalation of nickel salts, at least from occupational exposure, but it is relatively rare. There are insufficient data to allow a guideline value to be set for this response, but the panel was not aware of any confirmed reports of sensitisation from environmental exposure. Recent work with airborne particulates in mice may indicate effects at lower levels of exposure (approximately $0.1 \mu\text{g}/\text{m}^3$) but there are insufficient data to attribute these unequivocally to nickel or to assess the impact on humans.
157. From the rat studies it can be concluded that the NOAEL for exposures to the insoluble salts (oxide and subsulphide) is at least $0.11 \text{ mg}/\text{m}^3$ (NTP, 1996a,c). In the case of exposures to nickel sulphate (as hexahydrate) chronic active inflammation and fibrosis was seen at $0.06 \text{ mg}/\text{m}^3$ and above (NTP, 1996b). Female (but not male) mice also showed clear evidence of chronic inflammation at $0.06 \text{ mg}/\text{m}^3$, the lowest dose tested (NTP, 1996b). Thus, $0.06 \text{ mg}/\text{m}^3$ can be considered to be the lowest adverse effect level (LOAEL) for soluble nickel compounds in experimental animals.
 158. It is evident from studies *in vitro* that soluble nickel salts may have weak mutagenic potential and that this is probably due to the nickel ion. There are no robust data to indicate whether this potential is expressed *in vivo*. There is no substantial evidence for mutagenic potential of the less soluble salts. It is therefore plausible that a non-genotoxic mechanism, based on the formation of oxygen radicals and consequent sustained cell proliferation due to repair of oxidative damage, could account for the lung tumours seen. If this is the active mechanism then there is likely to be a threshold of effect.
 159. Based on the above there are two routes by which an air quality standard could be calculated.
 160. The inflammatory response in experimental animals is considered definitive (i.e. occurs at the lowest exposure levels) so the Panel considered that a value of $0.06 \text{ mg}/\text{m}^3$ should be taken as a LOAEL based on the results from the most sensitive study (NTP, 1996b). From examination of the effects seen at the next lower dose ($0.03 \text{ mg}/\text{m}^3$), it is likely that the “true” NOAEL will be close to this value. Thus, as a precaution the Panel considered that a factor of five should be adequate to account for the use of a LOAEL. The rats and mice were exposed six hours/day for five days/week (30 hours/week) so to account for continuous exposure a further factor of six should be applied. Finally to account for extrapolation from experimental animals to humans and to allow variability in individual sensitivity a factor of 100 (ie 10×10) was applied. (It is recognised that for minerals such as nickel this is likely to be over-cautious as the metabolic difference between species is likely to be small). This

- gives a value of $0.02 \mu\text{g}/\text{m}^3$. As less than 50% of atmospheric nickel is present as soluble salts and the NOAEL for the insoluble compounds is an order of magnitude higher the value should be doubled to $0.04 \mu\text{g}/\text{m}^3$.
161. An alternative is to base the standard on the observed incidence of respiratory tract tumours in humans. Seilkop and Oller (2003) provide a comprehensive summary and analysis of the data available from studies published before 2002. As stated above, workers in the nickel industry are usually exposed to nickel in a mixture of forms as well as other substances and there are no absolutely reliable data for long term concentrations of atmospheric nickel in the workplace. The available assessments of long term average exposure levels are based on full shift exposure measurements and the limitations of the measurement methodologies available mean that there is no information about short term peak concentrations during individual shifts. It is possible that respiratory irritation caused by unmeasured intense peaks in exposure is more important in the development of disease than mean exposure levels over a full shift.
162. The Panel considered that the measurements available from low risk/low exposure cohorts demonstrate that the reported excess cancer risk diminishes rapidly below a value of $1 \text{ mg}/\text{m}^3$ as a long term average concentration in workplace air. Statistically significant excess risks of lung cancer have, however, been reported in nickel refinery workers with mean exposures to $0.1\text{-}0.4 \text{ mg}/\text{m}^3$ (Anttila *et al.*, 1998) and alloy workers with exposures to $0.01\text{-}0.3 \text{ mg}/\text{m}^3$ (Redmond, 1984). Small excess risks have been also been reported in electroplaters exposed to mean concentrations of $0.01\text{-}0.08 \text{ mg}/\text{m}^3$ but these risks were not statistically significant (Pang *et al.*, 1996). From the data summary and accompanying exposure-response function model provided by Seilkop and Oller (2003), the Panel concluded that the value of $0.02 \text{ mg}/\text{m}^3$ could be taken as a LOAEL in humans. This is consistent with the findings of a more recent study by Grimsrud *et al.* (2002) who report statistically significant increased risks of cancer in workers with cumulative exposures to soluble nickel of $1.60 \text{ mg}/\text{m}^3 \times \text{years}$ or oxidic nickel of $1.67 \text{ mg}/\text{m}^3 \times \text{years}$; the equivalent long term mean exposure to either form of nickel over a 40 year working lifetime would be $0.04 \text{ mg}/\text{m}^3$. Given the apparent shallow dose-relationship at low concentrations a ten fold factor was applied for extrapolation from a LOAEL and a further ten fold factor for occupational to continuous exposure, including the higher respiratory dose rate experienced by children. A further ten fold factor to allow for "susceptible groups within the population" was applied as a precautionary step. This gives a calculated value for lifetime exposure of $0.02 \mu\text{g}/\text{m}^3$.
163. As both calculations produced similar results, the panel considered that the lower value ($0.020 \mu\text{g}/\text{m}^3$) should be adopted, as it is based on human data, which has a more serious outcome with increased incidence of cancer compared to the effects seen in animals. Soluble nickel is rapidly

excreted and the effects of insoluble nickel are seen at higher concentrations than those from the soluble salts. The guideline value is an annual average.

3.6 Recommendation

0.020 $\mu\text{g}/\text{m}^3$ total nickel compounds, in the PM_{10} size fraction, as an annual mean.

- 164. The panel recommends that an airborne concentration of all nickel compounds (measured as nickel) of 0.020 $\mu\text{g}/\text{m}^3$ (annual mean) should protect against the short and long-term effects of inhaled nickel.**

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Chapter 4

Beryllium

4.1 Background

4.1.1 Basic chemical information

165. Beryllium is a very light, but hard metal with a high melting point (1280°C). It has good electrical and thermal conductance and is resistant to corrosion. Its concentration in rocks of the earth's crust is variable but averages 3 mg/kg. Appreciable concentrations of beryllium occur in coals, with values generally ranging between 1 and 2 mg/kg (Reimann *et al.*, 1998) but sometimes, for example in poor quality brown coals from central Europe, as high as 30 mg/kg (Bouška, 1981). It has been suggested that just 1% of the beryllium in coal is volatilised during combustion (Kubizňáková, 1987) so that much of the element remains in the ash residue.
166. It is the inhalation of insoluble beryllium compounds which seems to cause the most serious health problems; these compounds include beryllium oxide and various alloys, the most important being copper-beryllium alloy. However, it seems likely that not all forms of beryllium-containing materials pose the same health risk. Wegner *et al.* (2000) studied beryl gemstone cutters and found little in the way of adverse health effects despite exposures as high as 2 µg/m³ beryllium. Similarly Deubner *et al.* (2001a) found that workers at a bertrandite [Be₄Si₂O₇(OH)₂] mine experienced no respiratory health problems. These authors suggest that in the absence of beryllium oxide particles, exposure to ore dusts of beryl and bertrandite or beryllium salts carries a lower risk of respiratory health effects. In another study Kreiss *et al.* (1993) found higher rates of chronic beryllium disease in workers in the beryllium ceramics industry where beryllium oxide is the essential component. Paustenbach *et al.* (2001) also suggest that beryllium oxide is the most hazardous form in industrial settings; in any case beryllium alloys always have some degree of oxide formation on exposed surfaces after machining.

4.1.2 Sources and concentrations of beryllium in the UK atmosphere

167. Much of the beryllium in the atmosphere probably derives from anthropogenic sources although the size of this contribution is disputed. In the USA it has been estimated that 97% results from coal combustion with 2.7% contributed by volcanic eruptions and the remaining 0.2% deriving from the production and industrial use of the element (Kolanz, 2001). However, others (Reimann *et al.*, 1998; Willis and Florig, 2002) suggest that the major contributor to atmospheric beryllium is soil dust.
168. The main sources of beryllium emissions to the air in the UK (Dore *et al.*, 2004) are reported to be road traffic (about 40%), domestic and other space heating (about 20%), non-road mobile machinery (about

- 10%) and refineries (about 10%). About three quarters of the emissions are associated with the combustion of liquid fuels and about one quarter with the combustion of solid fuels. Estimates of UK emissions are only available for the period from 2000 to 2004 and show no major changes over this period.
169. The National Atmospheric Emissions Inventory has only recently started to report emission estimates for beryllium. They are subject to considerable uncertainty and emission factors are only available for the combustion of solid and heavy liquid fuels; and not for industrial processes with the exception of iron and steel manufacture and a few others. The emission factors used have not been subject to any in-depth review. A limited review carried out for the 2003 inventory concluded that the emission factors for solid and liquid fuels are based on very few data and, in the case of coal, also require various assumptions to be made about, for example, the efficiency of particulate matter abatement in use by industry. It is possible that the emission factors for coal and oils might be out by a factor of five; if this were the case then coal, rather than oil, could be the major source.
170. The available data suggest that there is little industrial use of beryllium in the UK. Only one, small company uses beryllium oxide, in the manufacture of an electronic product. An estimated 50 companies (employing an estimated total of 500 employees) in the UK manufacture or machine products containing beryllium as an alloy. It is probable however that there is further use of beryllium alloys; this is anticipated to increase (Health and Safety Executive personal communication; data held on file).
171. In the absence of industrial contamination, ambient air generally contains very low or non-detectable concentrations of beryllium. Higher levels are generally found in urban air reflecting anthropogenic sources such as burning of fossil fuels; and in the vicinity of coal fired power stations or waste incinerators – presumably because the latter may be used for the disposal of the many electrical items (computers and mobile phones) that contain beryllium. Since it is fairly easily mobilised, beryllium in fly ash is a potential source of environmental contamination; concentrations vary from 1.6–46 mg/kg (Kubizňáková, 1987; Stadnichenko *et al.*, 1961). The highest ambient air levels have been recorded near factories and the like where beryllium is processed or beryllium-containing products are manufactured. Around a beryllium processing plant in Loraine, Ohio, USA, Eisenbud *et al.* (1949), found that within approximately 650 feet (212 metres) of the plant measured concentrations of beryllium were as high as 460 ng/m³, falling to 30 ng/m³ a mile (1.61 km) distant.

Table 4.1: Atmospheric concentrations of beryllium in polluted and unpolluted environments, various countries.

Site	Beryllium concentration (ng/m ³)	Data source
Rural USA	0.03 – 0.06	Ross <i>et al.</i> (1977)
Suburban USA	0.04 – 0.07	Ross <i>et al.</i> (1977)
Urban USA	up to 6.7	ASTDR (2002)
Urban Germany	0.06 – 0.33	Mueller (1979); Freise and Israel (1987)
In vicinity of coal-fired power station, Spain	up to 1.61	Boix <i>et al.</i> (2001)
In vicinity of Beryllium processing plant, USA.	up to 82.7	Sussman <i>et al.</i> (1959)
In vicinity (400m) of Beryllium processing plant, former USSR - no emission control	1000	Benko <i>et al.</i> (1980)

Comparison between these and earlier measurements suggests a marked reduction over time in levels of atmospheric contamination.

172. In the UK Harrison *et al.* (2003) measured beryllium in air concentrations in Birmingham between October 2000 and January 2001 in the PM₁₀ size range at a roadside location. The average concentration from 30 daily samples was 0.05 ng/m³, with individual daily concentrations ranging from 0.01-0.15 ng/m³. The beryllium was primarily within the finest size fraction sampled (< 0.2 µm aerodynamic diameter).

4.1.3 Human exposures

173. Human exposure can occur via inhalation, ingestion or skin contact. Inhalation represents the major pathway with regard to industrial exposure but dermal exposure through penetration of skin can lead to beryllium dermatitis and subcutaneous, granulomatous nodules. The role of dermal exposure as a route of sensitisation and disease is uncertain (Tinkle *et al.*, 2003; Day *et al.*, 2006).
174. By far the most important source of exposure is directly or indirectly through the workplace. Seventy five percent of beryllium is used in the production of copper-beryllium alloys (Cunningham, 2003) which are used extensively in the aerospace, telecommunications, computer, vehicle and oil/gas industries. Beryllium oxide is incorporated into a ceramic which is used in electronic circuitry, ignition systems and microwave ovens. Cases of berylliosis have been shown to occur in workers handling all insoluble beryllium-containing materials (Maier, 2002).
175. While urban exposures are probably higher than rural, it seems likely that non-occupationally exposed individuals are not exposed to high concentrations of atmospheric beryllium (Apostoli and Schaller, 2001).

176. Other, minor respiratory exposures include cigarette smoking although this is not considered to be important in the development of beryllium disease (Sawyer *et al.*, 2002). Beryllium may be used in the manufacture of dental bridges, crowns and plates; and in this form has occasionally resulted in allergic reactions in the mouth and gums. Similarly, it is unlikely that dermal exposure to beryllium will result from non-occupational exposure. While the beryllium containing gemstone beryl (including aquamarine and emerald) is used in jewellery, this mineral does not cause any dermal problems.
177. The concentrations of beryllium in drinking waters are generally very low in the UK; a study of British aquifers revealed a highest concentration of 1.02 µg/L beryllium (Edmunds and Trafford, 1993). Concentrations in foodstuffs are very variable but since most ingested beryllium is rapidly excreted, even those with high beryllium content are unlikely to induce any serious health effect in humans.

4.2 Toxicokinetics

4.2.1 Absorption

178. Inhalation is the major pathway into the body with beryllium subsequently absorbed through the lungs; there is, however, insufficient information to determine rates or degree of absorption (ATSDR, 2002) which in any case are likely to depend on the solubility of the inhaled compound.
179. When insoluble or low-solubility beryllium-containing particles are inhaled most are thought to be removed by mucocilliary transport to the gastrointestinal tract. Some however is transferred to the regional lymph nodes and pulmonary interstitium where it may be retained for many years after exposure (Maier, 2002; Sawyer *et al.*, 2005). This retained beryllium is slowly solubilised and is the source of adverse health effects.
180. It is generally believed that there are two phases – one rapid, one slow - of beryllium removal from lungs, probably corresponding to the removal of soluble and insoluble components respectively. In animal models the half-life for rapid removal is between 1-60 days, while for the slow phase it is in the range of 0.6-2.3 years (WHO/IPCS, 2001). Rosenman *et al.* (2005) found that exposed workers without chronic beryllium disease had been exposed to higher concentrations of soluble beryllium – and thus had had a lower retained body burden - than those with disease.

4.2.2 Distribution

181. Beryllium that is absorbed after inhalation is transferred to tracheal lymph nodes and ultimately to the skeleton, the main site for storage (WHO/IPCMS, 2001). In a rodent model where rats were exposed by inhalation to radioactively labelled beryllium in the form of soluble salts, measurements after 408 hours exposure suggested that 92% of the total body radioactivity was in excreta with 6.8% retained in the skeleton. Small amounts are transferred to the liver and other organs

(ASTDR, 2002). Beryllium may bind to the iron-transport protein ferritin and be transported back to the lung where it can be taken up by lung macrophages so promoting beryllium-antigen formation (Sawyer *et al.*, 2004); it is postulated that this action is the cause of chronic beryllium disease many years after exposure has ceased.

182. Beryllium can form complexes with both adenosine triphosphate (ATP) and adenosine diphosphate (ADP) (Boukhalifa *et al.*, 2004), as well as with endogenous proteins such as ferritin and transferrin (Price and Joshi, 1983; Sawyer *et al.*, 2004). Sawyer *et al.* (2002) quote literature data suggesting that beryllium interacts with nuclear acidic proteins, G proteins and protein kinases and interferes with protein phosphorylation; in addition it inhibits the activities of regulatory enzymes.

4.2.3 Metabolism

183. Beryllium and its compounds seem not to be biotransformed, although it is likely that soluble salts can in part be converted to insoluble forms in the lung (Reeves and Vorwald, 1967).

4.2.4 Elimination

184. Almost all (98%) ingested beryllium is excreted via faeces; much inhaled low-solubility beryllium is transferred from the lung to the gastrointestinal tract and similarly excreted. Renal excretion also occurs after inhalation and is probably important for soluble beryllium, and that solubilised in the lung; workers exposed to elevated levels of atmospheric beryllium have higher concentrations in urine than subjects not exposed (ATSDR, 2002; Apostoli and Schaller, 2001). However, some beryllium is thought to remain in the lung for several years where it will slowly dissolve (Maier, 2002), move into the blood stream and subsequently be excreted. Beryllium inhalation can cause lung damage and consequently decrease the ability of the lung to clear the particles (ASTDR, 2002). The half-life of inhaled beryllium in animals varies greatly, with much of the variation thought to be due to its chemical form (ATSDR, 2002). The half-life of beryllium stored in bone is around 450 days.
185. There is no information on the toxicokinetics or toxicity of beryllium in children.

4.3 Health Effects

4.3.1 Acute health effects

186. Short-term respiratory exposures to high concentrations of beryllium salts and particulate beryllium oxide can induce an acute pneumonitis which is sometimes lethal. There is little information on the minimum levels necessary to cause this though a 1940s study suggests that all affected workers were exposed to $>0.1 \text{ mg/m}^3$ beryllium generally as soluble beryllium sulphate or fluoride (Eisenbud *et al.*, 1948). The occurrence of acute beryllium disease is currently very rare; only odd

cases resulting from accidental exposure have been recorded in more recent times (Eisenbud and Lisson, 1983).

187. Experiments with animals subjected to high doses of soluble beryllium salts result in a relatively high death rate. Animals exposed to beryllium oxide have a lower mortality, due probably to the lower solubility of the oxide. In studies of rats inhaling soluble beryllium sulphate at concentrations of 4.3 mg/m³ or 2.59 mg/m³, all died within 14 and 18 days respectively; of rats exposed to 31 mg/m³ beryllium as beryllium oxide, 10% died. Of 74 rats exposed for 50 minutes to aerosolised beryllium metal at a concentration of 0.8 mg/m³, 20 died 12-15 days after exposure. There seems to be inter-species variation in susceptibility with rats and monkeys being more sensitive to acute beryllium exposure than hamsters and guinea pigs (ATSDR, 2002).

4.3.2 Sub-chronic effects – beryllium sensitisation

188. Immunological ‘delayed-type’ sensitisation to beryllium may be present in the absence of detectable disease. It is believed to arise following inhalation of beryllium but dermal exposure may also be important. Sensitisation is identified using a specialised test - the beryllium-stimulated lymphocyte proliferation test (BeLPT) – on blood or lung fluid samples. Beryllium sensitisation does not seem to be dependent on the degree of exposure (Willis and Florig, 2002) and may occur after only brief contact with beryllium compounds (Viet *et al.*, 2000). There is probably an important genetic component to individual susceptibility; the leukocyte antigen, HLA-DPB1 Glu⁶⁹ has been found in a higher than expected proportion of sensitised individuals and in those suffering from chronic beryllium disease (Richeldi *et al.*, 1997; Saltini *et al.*, 2001; Amicosante *et al.*, 2002; McCanlies *et al.*, 2003, 2004). Estimates of the proportion of individuals who are so predisposed vary widely between 1-15%.
189. It has also been suggested that beryllium can cause an allergic reaction on skin. Sawyer *et al.* (2002) are of the opinion that dermatitis caused by beryllium contact – for example through dental bridges - is in fact a beryllium sensitive reaction. Tinkle *et al.* (2003) showed that beryllium oxide caused sensitisation in mice due to particles penetrating the skin. These workers postulate that skin sensitisation of workers exposed to beryllium containing materials could be an added factor to respiratory exposure.

4.3.3 Chronic effects

190. Airborne beryllium exposure may give rise to a granulomatous, interstitial lung disease – chronic beryllium disease (CBD) or ‘berylliosis’ - that has many similarities to sarcoidosis. In almost all instances it is accompanied by evidence of beryllium sensitisation. The disease has a long latency, becoming apparent many years (up to 40) after first exposure and any time between a few months to decades after sensitisation. It is incurable and when severe can result in terminal respiratory failure.

191. On review of the literature, McCanlies *et al.* (2003) suggest that between 36% and 100% of sensitised employees show signs of CBD. Estimates of the annual incidence of progression from sensitisation to disease range from about 5% to 10% (Maier, 2002; Newman *et al.*, 2005). Progression beyond sensitisation might also have one or more genetic determinants (Saltini *et al.*, 2001; Maier *et al.*, 2003).
192. There are no animal models of the disease and virtually all of the information on CBD derives from studies of workforces, in most cases in the USA. Workplace prevalence figures for both sensitisation and berylliosis vary (see Table 4.2) in part because of different study designs and methods of detecting disease but probably also because of variable exposures.

Table 4.2: Prevalences of beryllium sensitisation and chronic beryllium disease in beryllium exposed workers in the USA.

Source	Site	No. of subjects	Beryllium sensitisation	Beryllium sensitisation and CBD
Kreiss <i>et al.</i> (1997)	Beryllium metal, alloy, and oxide production plant	627	9.4%	4.6%
Stange <i>et al.</i> (1996)	Nuclear weapons facility	4,397	1.8%	0.66%
Stange <i>et al.</i> (2001)	Nuclear weapons facility	5,173	4.54%	1.57%
Kreiss <i>et al.</i> (1996)	Beryllium ceramics plant	136	5.9%	5.7%
Henneberger <i>et al.</i> (2001)	Beryllium ceramics plant	151	9.9%	5.3%
Rosenman <i>et al.</i> (2005)	Beryllium production plant	577	14.6%	7.6%

193. The risk of chronic beryllium disease may increase with increasing exposure although it has not always been easy to demonstrate this (Viet *et al.*, 2000; Rosenman *et al.*, 2005). Exposure to particles less than 10 μm in mean diameter may be especially important (Kent *et al.*, 2001; Kelleher *et al.*, 2001); Stefaniak *et al.* (2003) also suggest that the total surface area of the beryllium containing substance is a better measure of relevant exposure. The chemical form of beryllium seems also to be important with beryllium ore minerals such as beryl and bertrandite posing minimal risk. Soluble beryllium compounds are less problematic than insoluble ones such as beryllium, the metal, its alloys and beryllium oxide, especially where the last is produced at higher temperatures (Maier, 2002).
194. Machinists – who are exposed to greater concentrations of respirable beryllium-containing particles – have a higher risk of chronic beryllium disease than other employees (Martyny *et al.*, 2000; Stange *et al.*, 2001; Kreiss *et al.*, 1996; Kelleher *et al.*, 2001; Welch *et al.*, 2004; Newman *et al.*, 2005). Several studies however, have identified both

sensitisation and disease among non-production workers including administrative staff (Kreiss *et al.*, 1993; Maier, 2002; Stange *et al.*, 2001; Rosenman *et al.*, 2005).

195. There is an increased incidence of hypercalcaemia, hypercalcuria and renal stones in patients with CBD. These probably reflect the granulomatous nature of the lung disease. A mortality study of workers at seven beryllium processing plants found an increased incidence of death due to renal causes (Ward *et al.*, 1992).
196. Reductions in levels of airborne beryllium have not necessarily been accompanied by concomitant reductions in the incidence of disease; dermal exposures – and even ingestion - have therefore been considered as alternative, important routes of exposure (Tinkle *et al.*, 2003; Deubner *et al.*, 2001b). In humans, where skin has been penetrated by beryllium or beryllium oxide, granulomatous lesions may develop (Sawyer *et al.*, 2002). Contact dermatitis has been described in workers exposed to airborne beryllium salts (ATSDR, 2002) and in some individuals fitted with dental bridges containing beryllium (Sawyer *et al.*, 2002).

4.3.4 Genotoxicity

197. Laboratory studies of the genotoxicity of beryllium have been contradictory (Gorden and Bowser, 2003). Mutation and chromosome aberration assays on bacteria have generally given negative results. Some studies on mammalian cells *in vitro* have indicated that beryllium salts have caused sister chromatid exchange and possible chromosome aberration (IARC, 1993); however, Anderson (1983), did not find any sister chromatid exchange on beryllium sulphate treatment of human lymphocytes. The International Agency for Research on Cancer report on one study using beryllium chloride where gene mutation occurred in mammalian cells; and in another study of cultured mammalian cells low temperature beryllium oxide was found to cause breaks in single strand DNA (IARC, 1993). An *in vivo* study on mice subjected to beryllium sulphate found that no micronuclei were induced in bone marrow (IARC, 1993). Some of the contradiction in this evidence is probably due to the use and preparation of different forms of beryllium.

4.3.5 Carcinogenicity

198. Beryllium has been classed as a Group 1 human carcinogen by the International Agency for Research on Cancer (IARC, 1993). The US Department of Health and Human Services (USDHHS, 2003) also lists beryllium and its compounds as known human carcinogens. The American College of Governmental Industrial Hygienists (ACGIH, 2001) lists beryllium as a confirmed carcinogen. However, the US Environmental Protection Agency lists beryllium in group B1, making it a probable human carcinogen (USEPA, 1998).
199. Increased risks of death from lung cancer have been reported in a small number of occupational cohorts from the USA. In each there is

limited – if any – control for confounding exposures (especially cigarette smoking) and disease latency.

200. The earliest studies were of employees in beryllium processing facilities in Ohio and Pennsylvania, USA and were carried out from the late 1960s through to the 1980s (see references in ATSDR, 2002). In 1991 Steenland and Ward (1991) reported the mortality experience of 689 employees on the US Beryllium Case Registry; 34% of whom had acute pulmonary disease and 64% CBD. There were 28 deaths from lung cancer. The risk was higher among patients with acute beryllium disease, suggesting that lung cancers are more likely to be caused by high exposures.
201. In 1992, Ward *et al.* (1992) reported small increases in the rates of lung cancer in two of seven processing plants. Both had opened prior to 1950, when there was little limitation on airborne beryllium concentrations in the workplace. In four plants opened after 1950 no increased lung cancer rates were found. The overall standardised mortality ratio (SMR) was 1.26 (95% confidence interval 1.12-1.42); higher rates of lung cancer were found in those employed for at least a year with a 30-year latency period (SMR 1.46).
202. The only study in which there are detailed exposure estimates is the nested case-control analysis of the above cohort (Sanderson *et al.*, 2001) in which 142 deaths from lung cancer were analysed. For cancers with a ten year lag, the estimated odds ratios by exposure category were as follows:

Table 4.3: Risk estimates (odds ratios) of lung cancer in a cohort of USA workers exposed to beryllium

average airborne exposure intensity	odds ratio	p value
<2 ug/m ³	1	
2-20 ug/m ³	4.07	<0.01
>20 ug/m ³	4.17	<0.01

The methodology of this work was subsequently criticised on behalf of the US beryllium industry (Deubner *et al.*, 2001a).

203. What evidence is available suggests that the above findings can not be attributed entirely to the confounding effects of cigarette smoking. There is no information concerning any potential interaction between smoking and beryllium exposure in the induction of lung cancer.
204. Animal experiments have shown that with high doses of inhaled beryllium salts rats and monkeys developed lung cancers. Beryllium metal in high dose caused 64% of an exposed group of rats to develop lung cancer. While exposure to beryl ore caused cancers in rats, this was not the case among both rats and hamsters exposed to bertrandite ore. In general animal experiments have been criticised for

using very high exposures (ATSDR, 2002); however, they seem to confirm the carcinogenicity of beryllium.

4.3.6 Reproductive and development toxicity

205. There are no studies of reproductive or development toxicity after beryllium inhalation by humans or animals (ATSDR, 2002). A study on male and female rats intratracheally injected beryllium oxide, prior to mating, resulted in no consistent effect on reproduction (Clary *et al.*, 1975). Limited effects were observed on the development of rat fetuses when pregnant females were intratracheally injected with beryllium chloride and beryllium oxide: there was some increase of fetal mortality and decrease of fetal body weight with an increased risk of internal abnormalities.

4.4. Evaluations and recommendations by other organisations

206. Most animal experiments with airborne beryllium have involved large doses and subsequently determined lowest observable adverse effect levels (LOAEL) have been very much higher than those found in studies on humans (USEPA, 1998; ATSDR, 2002).

4.4.1 Chronic beryllium disease

207. Following the identification of CBD in the 1940s, the first occupational exposure limit (OEL) was introduced by the US Atomic Energy Commission in 1949; an 8-hour OEL for beryllium was established at 2 $\mu\text{g}/\text{m}^3$. This standard was not based on the risk of CBD but on the values used for other toxic metals (cadmium, mercury and thallium); however, it was subsequently widely adopted.
208. It became clear that while an OEL of 2 $\mu\text{g}/\text{m}^3$ resulted in a decrease of beryllium exposure it did not provide complete protection for workers. Subsequently a small number of studies have identified a human LOAEL; some of these are listed in Table 4.4.

Table 4.4: Lowest observable adverse effect levels values from data in USEPA (1998) and ATSDR (2002)

Study	Beryllium source	LOAEL
Kreiss <i>et al.</i> (1996)	Ceramic manufacture from beryllium oxide	0.55 $\mu\text{g}/\text{m}^3$
Stange <i>et al.</i> (1996)	Nuclear weapons facility	1.04 $\mu\text{g}/\text{m}^3$
Cullen <i>et al.</i> (1987)	Precious metal refinery – beryllium oxide	0.52 $\mu\text{g}/\text{m}^3$
Cotes <i>et al.</i> (1983)	Beryllium manufacturing plant – beryllium oxide	0.1 $\mu\text{g}/\text{m}^3$

209. Eisenbud (1998), using the earlier Lorain data, derived an OEL of 0.2 $\mu\text{g}/\text{m}^3$ as the lowest concentration protecting individuals from CBD. Employees at a copper-beryllium alloy factory did not, at cross-

sectional survey, have either sensitisation or CBD if they worked in areas where the levels of beryllium 'rarely' exceeded $0.2 \mu\text{g}/\text{m}^3$ (Schuler *et al.*, 2005).

210. A case-control study of employees at a US beryllium machining plant reported that no workers with a lifetime workplace time-weighted exposure of $<0.02 \mu\text{g}/\text{m}^3$ developed either beryllium sensitisation or CBD (Kelleher *et al.*, 2001). Similarly the results of beryllium lymphocyte transformation testing are reported to be unaffected by exposures of $<0.01 \mu\text{g}/\text{m}^3$ (Yoshida *et al.*, 1997).
211. The study by Eisenbud *et al.* (1949) is the most complete study of non-occupationally exposed populations. In this study centred around the Lorain processing plant in Ohio, USA, 10,000 residents were evaluated for CBD. In the initial study 11 cases of CBD were identified along with three more in a follow-up study (Sterner and Eisenbud, 1951). One case was attributed to dust from contaminated work clothes; the rest to exposure to atmospheric beryllium. All lived within $\frac{3}{4}$ of a mile (1.21 km) of the plant. It was apparent that the percentage of the local population who were suffering from CBD was similar to that found in workers from the beryllium plant. This was suggested to be due to finer beryllium-containing particles (mainly beryllium oxide) being transported from the factory. A LOAEL of between $0.01 \mu\text{g}/\text{m}^3$ and $0.1 \mu\text{g}/\text{m}^3$ was estimated. Wambash and Tuggle (2000) using the same data to statistically model an OEL derived a figure of $0.1 \mu\text{g}/\text{m}^3$. It should be noted that the specificity of the diagnoses in this early study must be questioned.
212. The original OEL was based on total atmospheric beryllium. It has been suggested that the OEL should take cognisance of particle size and surface area (Kolanz *et al.*, 2001; Stefaniak *et al.*, 2003).
213. The USEPA (1998) lists regulations from several states in the USA:

Table 4.5: Regulations for concentrations of beryllium in air for some states of the USA from USEPA (1998)

State	Allowable concentration
North Carolina	$4.1 \text{ ng}/\text{m}^3$
Vermont	$1.3 \text{ ng}/\text{m}^3$
Washington	$0.42 \text{ ng}/\text{m}^3$

214. The ACGIH (2001) document on beryllium recommended a Threshold Limit Value-Time Weighted Average (TLV-TWA) of $2.0 \mu\text{g}/\text{m}^3$ beryllium, to protect against operational exposure, but stated that the figure was under review. However, in a recent document (ACGIH 2006), the proposed TLV-TWA is significantly lower at $0.05 \mu\text{g}/\text{m}^3$ inhalable particulate mass. This is in response to the studies which have demonstrated that susceptible individuals are at risk at low atmospheric concentrations of beryllium and that inhalation of respirable particulate beryllium substantially increases the risk of developing sensitisation and CBD.

215. The USA Occupational Safety and Health Administration (OSHA) currently list a Permissible Exposure Limit (PEL) of $2 \mu\text{g}/\text{m}^3$ as an eight-hour time-weighted average (TWA) for beryllium and its compounds. This is accompanied by an acceptable ceiling concentration of $5 \mu\text{g}/\text{m}^3$. Exposures are allowed to exceed $5 \mu\text{g}/\text{m}^3$ (but never exceed $25 \mu\text{g}/\text{m}^3$) for a maximum of 30 minutes during an 8-hr shift but there must be corresponding periods of lower exposure such that exposure for the 8-hr shift does not exceed the 8-hr TWA PEL. OSHA is in the process of re-evaluating these limits owing to concerns that they may not be adequate to protect health (OSHA, 2005).
216. In the UK the maximum exposure limit (MEL) assigned for beryllium and its compounds is $2 \mu\text{g}/\text{m}^3$, averaged over an 8-hour period (HSE, 1995). Maximum Exposure Limits are occupational exposure limits set under the Control of Substances Hazardous to Health (COSHH) Regulations (2002 as amended).

4.4.2 Lung cancer

217. The USEPA (1998) has estimated the unit health risk from lung cancer due to continuous exposure to beryllium to be 2.4×10^{-3} per $\mu\text{g}/\text{m}^3$. On this basis they have further estimated that an individual inhaling in an atmosphere containing $0.4 \text{ ng}/\text{m}^3$ beryllium throughout life, would theoretically have no more than a one in a million increased chance of lung cancer; while an individual spending a lifetime inhaling an atmosphere containing $4 \text{ ng}/\text{m}^3$ beryllium, would not have more than a one in a hundred thousand increased chance of developing lung cancer.
218. Using the EPA figures Willis and Florig (2002) suggest that for an individual exposed to $2 \mu\text{g}/\text{m}^3$ of beryllium for a 2,000-hour work year and a 40-year working life, the lifetime lung cancer risk would be 0.0005, which is an order of magnitude smaller than that of CBD for sensitised individuals. These authors further suggest that the lifetime lung cancer mortality rate for an individual living in close proximity to a beryllium-emitting industrial site, which is in compliance with the EPA limit for concentrations around beryllium plants ($0.01 \mu\text{g}/\text{m}^3$) will be approximately 2×10^{-5} . McCanlies *et al.* (2003) also suggest that the risk of CBD in sensitised individuals vastly exceeds that of lung cancer.

4.5. Justification for air quality guideline

219. Because the risks of sensitisation and CBD are apparent at far lower exposures, it seems appropriate to base a guideline on these rather than on the risk of lung cancer.
220. Use of a no observed adverse effects level (NOAEL) of $0.02 \text{ ug}/\text{m}^3$ for both sensitisation and CBD (Kelleher *et al.*, 2001) with division by ten to allow for the greater exposure duration of the general public and a further ten to allow for the presence of susceptible individuals would produce a guideline value of $0.2 \text{ ng}/\text{m}^3$.

221. The Panel recognises the uncertainties over the time period required to induce a disease characterised by sensitisation but considers that an annual averaging time would be appropriate.

4.6. Recommendation

0.2 ng/m³ total particulate beryllium in the PM₁₀ size fraction, as an annual average.

222. **This value is close to the highest level measured in a UK roadside site. Given the paucity of data, the Panel recommends that further and more extensive measurement of airborne particulate beryllium be made in urban and industrial centres across the UK to establish whether traffic or industrial sources are the more important.**

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Chapter 5

Chromium

5.1 Background

5.1.1 Basic chemical information

223. Chromium is a metallic element. The metal is hard and dense and is resistant to chemical attack because a protective film of chromium trioxide forms on the surface. It forms stable compounds, which are widespread in the environment. It is relatively abundant in soil and rocks, but the only important ore is ferrochromite. Chromium comprises about 200 mg/kg of the Earth's crust. The median concentration in UK soils is about 39 mg/kg: concentrations in polluted soils are highly variable but may be as high as 10,000 mg/kg (Alloway, 1995).
224. Chromium metal is stable but occurs in the free form only as a result of industrial production. In the environment, chromium exists predominantly in two oxidation (valence) states. Trivalent chromium (Cr(III)) is the more stable and thus more abundant. Most Cr(III) compounds are insoluble in water. Hexavalent chromium compounds (Cr(VI)) are chiefly produced by industrial processes, and are generally more soluble in water than the Cr(III) compounds. Other oxidation (valence) states are known - divalent, tetravalent and pentavalent forms - but are unstable. An exception is the tetravalent chromium dioxide (CrO₂), which finds wide use in magnetic recording tapes.
225. Trivalent chromium is an essential nutrient for humans and animals, where it potentiates the action of insulin, assisting the metabolism of glucose, protein and fat. Living plants and animals absorb the Cr(VI) form in preference to Cr(III), but once absorbed, it is reduced to the stable Cr(III) state.
226. Chromium compounds are used for chrome plating, manufacture of dyes and pigments, leather tanning, wood preserving (copper-chrome-arsenate is used as a timber treatment), drilling mud, rust corrosion inhibitors, textiles and copy machine toners (ATSDR, 2000). Other uses include incorporation in metal alloys.

5.1.2 Sources of chromium in the UK atmosphere

227. Because of its presence in the earth's crust, chromium exists in a range of geological materials and is widespread in natural dusts. The main natural sources of airborne chromium are forest fires and, perhaps, volcanic eruptions. Man-made sources include all types of combustion and emissions by the chromium industry. It may be assumed that all of the chromium in air emitted from combustion sources is present as particulate chromium and is associated with the fine particulate fraction. Chromium

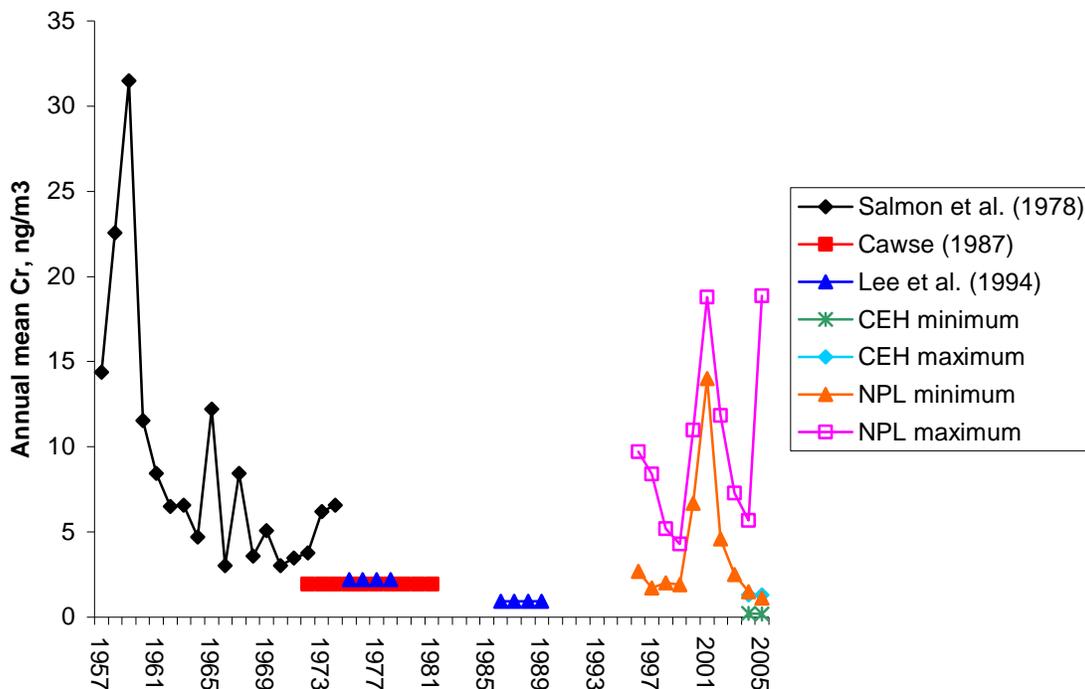
- from metallurgical production is usually in the Cr(III) or the metallic (zero) state. During chromate production, chromate dusts can be emitted. Aerosols containing chromic acid can be produced during the chrome-plating process.
228. The chemical forms of chromium in the air are poorly understood but chromium trioxide (CrO₃) may be the most important single compound (Sullivan, 1969). However it should be assumed that airborne chromium exists partially in the Cr(VI) form. Hexavalent chromium is subject to reduction to the Cr(III) form in the presence of other pollutants such as hydrogen sulphide, iron salts, bisulphites, oxides of nitrogen and organic material, which may also be emitted from the same sources. Kimbrough *et al.* (1999) estimated that the half life of Cr(VI) in the atmosphere ranges from 0.7-4.8 days.
229. Estimates of the comparative concentrations in air of Cr(III) and Cr(VI) are uncertain, in part because the ratio is variable and dependent on the source of chromium. In the UK it is likely that less than 20% of emissions are of Cr(VI), those with the higher proportions from chromium-using industries (Passant, 2006). The proportion of Cr(VI) in ambient air may be lower than that measured in emissions. Data from Canada, quoted by Rowbotham *et al.* (2000), suggest that Cr(VI) constitutes between 3 and 8% of total airborne chromium in that country. Keiber *et al.* (2002) found that about half of the chromium in rainwater in the USA was in water soluble form and of this there were approximately equal concentrations of Cr(VI) and Cr(III). As most of the insoluble chromium is likely to be present as Cr(III), this implies that the Cr(III)/Cr(VI) ratio in air was about 3:1.

5.1.3 Ambient concentrations

230. Chromium occurs in the air of non-industrialised areas in concentrations of less than 100 ng/m³ (WHO, 1988).
231. The main sources of chromium emissions to the air reported in the UK National Atmospheric Emissions Inventory for 2004 include emissions from the chemicals and iron and steel industries, power stations and the combustion of treated wood. Combustion of coal in power stations, industry and for domestic heating contributed 12% of the national total in 2004. Emissions from the combustion of wood treated with copper-chromium-arsenic preservatives were estimated to contribute 21%, although this latter estimate is extremely uncertain as chromium may not be volatilised during combustion to the same extent as arsenic. Process emissions from the chromium chemicals industry contributed 19%.
232. UK emissions of chromium are estimated to have declined by 83% between 1970 and 2002 as a result of reductions in chromium emissions from power stations, industry, domestic heating, industrial processes and waste incineration.

233. Figure 5.1 shows the available annual mean total particulate concentrations of chromium at rural sites from 1957 to 2005. After a peak in the 1960s levels at Harwell fell to the 1980s. For recent years the figure shows the range of values measured at monitoring sites in the national networks. Rural concentrations for recent years are close to or below this level at most locations but higher than other rural sites at Eskdalemuir (illustrated as NPL minimum on the graph, 3.3 ng/m³ in 2005), but much lower at the remaining rural sites with available measurements (0.2 to 0.7 ng/m³ in 2005). The reason for the higher measured rural concentration at Eskdalemuir is unclear but it is still well within the range of measured concentrations in urban areas.

Figure 5.1: Time history of the available annual mean total particulate chromium concentrations in rural air from 1957 through to 1989 for Harwell, Oxfordshire (Cawse, 1987; Lee *et al.* 1994; Salmon *et al.* 1978) and the maximum and minimum values measured in the national monitoring networks from 1996 to 2005 (NPL, 2006; CEH, 2006).



5.1.4 Human Exposures

234. Non-occupational human exposures to chromium are difficult to quantify. Exposure is widespread due to occurrence in air, water and soil. It is present in essentially all biological materials that have been examined, and thus is also consumed in food, although the trend to consumption of

- highly processed foods has led to a reduced intake by this route. This, coupled with the consumption of relatively high levels of sugar (which stimulates excretion of chromium) may lead to potentially serious dietary deficiency of chromium (Anderson, 1981).
235. Intake of chromium in the diet accounts for most of the non-occupational exposure. The wide variation in chromium content of food is the main reason for the difficulty in estimating intakes overall. Foods rich in chromium include meat, vegetables and unrefined sugar while fish, vegetable oils and fruit contain smaller amounts. The most available form of chromium in the diet is found in yeast, liver and meats (Langård and Norseth, 1979).
236. Chromium concentrations in drinking water have been measured in several countries and are almost always below (often well below) 0.005 mg/l. Thus an adult consuming 2 l/day would derive no more than 0.01 mg/day of chromium from this source. Dietary chromium is normally considered to be in the Cr(III) form as Cr(VI) is reduced in the presence of organic material. The speciation in drinking water is less certain; at least some of the intake from this source could be in the form of Cr(VI).
237. Wind blown soils and dusts provide a source of chromium in the atmosphere, but based on typical concentrations of chromium in surface soils, these are unlikely to generate annual concentrations as high as 1 ng/m³ except in areas of significant industrial contamination.
238. Although chromium is present in cigarettes at up to 390 µg/kg (Schroeder *et al.*, 1962) there are no published estimates of total intake from this source. However assuming complete absorption from 25 g tobacco daily, this would account for 10 µg/day, so it is unlikely that this will contribute significantly to the overall intake. However, it should be noted that this is possibly in the Cr(VI) form and in this context may be significant. Other potential sources such as wood preservatives, pica and residence in neighbourhoods with industrial contamination are only minor contributors to exposure. In the UK average daily intakes from ambient air are estimated to range from 0.0001 to 0.0006 µg/day, (based on values from DETR, 1997), but this may include a proportion of Cr(VI).
239. Occupational exposures to chromium and chromates have been measured during chromate and chrome pigment production, chrome plating, ferrochromium and chrome alloy production, leather tanning and gold mining. Average exposures measured range from 0.04 to 0.5 mg/m³.
240. Rowbotham *et al.* (2000) estimated the daily intake of total chromium for adults and children by inhalation and compared these with ingested chromium (Table 5.1). The assumptions made were that:
- adults breathe 20 m³, and children 8.7 m³, of air per day.
 - mean airborne particulate total chromium concentration for rural sites are 0.9 to 12 ng/m³ and for urban sites 4.1 to 17.2 ng/m³.

Table 5.1: Estimated range of daily intakes of chromium by inhalation, adults and children UK.

	Daily intake (μg) by inhalation
urban adult	0.08-0.34
rural adult	0.02-0.24
urban adult (smoker)	0.14-0.6
urban adult (passive smoker)	0.14-0.6
urban child	0.04-0.15
rural child	0.01-0.1

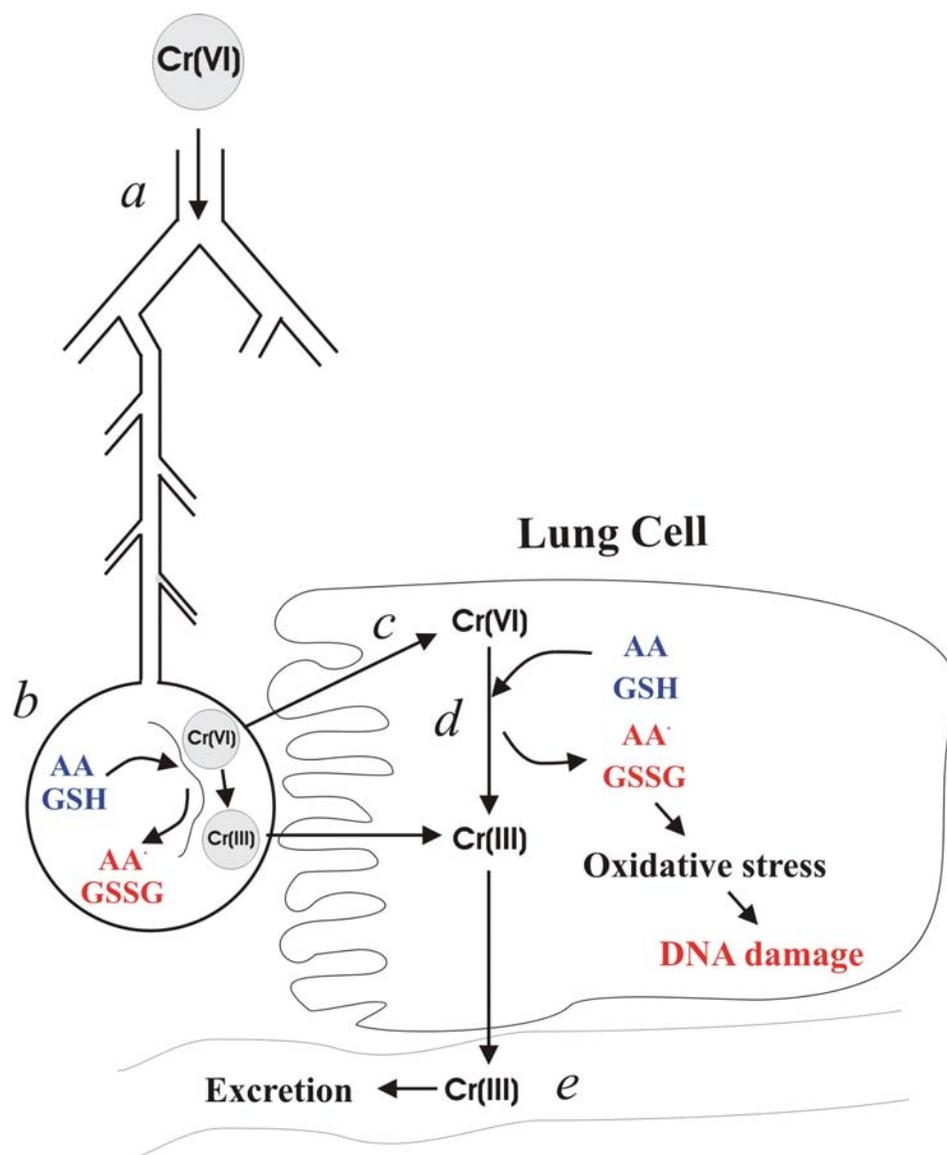
241. Rowbotham *et al.* (2000) also estimated the daily intake of Cr(VI) from inhalation, assuming that Cr(VI) constitutes between 3 and 8% of total airborne chromium. Inhaled intake of Cr(VI) for an urban child was between 0.001 and 0.01 $\mu\text{g}/\text{day}$. These figures compare with 0.002 and 0.03 $\mu\text{g}/\text{day}$ for an adult.

5.2 Toxicology

5.2.1 Pulmonary Absorption

242. Pulmonary absorption of chromium is influenced by a number of factors including size, oxidation state and solubility of the chromium particles. Absorption of inhaled chromium is demonstrated by its presence in other compartments such as blood and urine.
243. Hexavalent chromium compounds penetrate the alveoli more readily than trivalent compounds (CEPA, 1994). This process is described in detail in Figure 5.2.

Figure 5.2: Chromium - pulmonary absorption, metabolism & excretion (a) chromium containing particles or fumes may be inhaled (b) hexavalent chromium, Cr(VI), the carcinogenic form of chromium is reduced to Cr(III) by low molecular weight reductants such as ascorbic acid and glutathione in epithelial lining fluid. (c) any remaining Cr(VI) is transported into cells via the anion transport channel along a concentration gradient and (d) inside the cell reacts with reductants which leads to the formation of reactive oxygen species (ROS). The product, Cr(III) is less reactive and is subsequently released into the blood and excreted via the urine (e) involvement of other reductants can lead to carbon and sulphur radical formation that can also lead to tissue damage through oxidation of cellular targets such as proteins and DNA.



5.2.2 Metabolism

244. Any Cr(VI) reaching the blood is taken up by erythrocytes and reduced to Cr(III) by glutathione. Thereafter it may react with other cell components and is gradually released into the circulation where they bind to plasma proteins (USEPA, 1998).

5.2.3 Tissue distribution and excretion

245. Absorbed chromium travels around the body absorbed to plasma proteins and is taken up by a range of tissues including bone, liver, kidney and spleen (USEPA, 1998).
246. Absorbed chromium is eliminated largely in the urine with most of the unabsorbed portion in faeces (CEPA, 1994). The hair and nails are also minor pathways of excretion (Defra and EA, 2002).

5.3 Health Effects

5.3.1 Acute effects

5.3.1.1 Animal studies

247. Trivalent and hexavalent chromium can result in toxicity following oral, inhalation and dermal exposures. Acute oral toxicity in animals increases with increasing water solubility. Oral LD50 ranges for trivalent compounds range from 140-522 mg/kg and hexavalent compounds range from 13-795 mg/kg (Government of Canada, 1994). Acute toxic effects in rats and mice exposed to high single doses of Cr(VI) include gastric ulcerations, pulmonary congestion, gastrointestinal oedema, diarrhoea and cyanosis (von Burg and Liu, 1993).
248. In rats, LC50 values for inhaled, highly soluble chromium hexavalent compounds are in the range of 33-65 mg/m³ (von Burg and Liu, 1993). Associated effects include inflammatory responses and altered macrophage morphology.
249. Hexavalent chromium compounds can cause severe eye and skin irritation which can lead to ulceration. LD50 values for acute dermal exposure range from 400-677 mg/kg in rats. Associated effects include necrosis of the application site, diarrhoea, hypoactivity, dermal oedema and inflammation.

5.3.1.2 Human studies

250. Massive inhalations of chromium-containing fume can cause irritant damage to the upper and lower respiratory tracts. A study of ten volunteers exposed 'briefly' to CrO₃ reported nasal irritation above concentrations of 2.5 µg/m³ (Kuperman, 1964).

5.3.2 Chronic and sub-chronic effects

5.3.2.1 Animal studies

251. In studies involving rats fed up to 1000 times the daily human intake of chromium no toxic effects have been reported (Anderson, 1997) although decreased testicular enzyme activity has been noted (von Burg and Liu, 1993).
252. Following inhalation, immune system effects have been observed in animals exposed to both trivalent and hexavalent chromium. Responses included increased macrophage activity, total serum immunoglobulin content and antibody response (von Burg and Liu, 1993).

5.3.2.2 Non-malignant effects

253. Hexavalent chromium is a dermal irritant and sensitiser that can induce and provoke a delayed-type allergic contact dermatitis; sensitisation is identified through patch testing of the skin. These outcomes are not uncommon in several occupational settings including chrome-plating, leather tanning, and work involving repeated skin contact with wet cement. It is estimated that 0.08% of the USA population is sensitised in this way (Proctor *et al.*, 1998).
254. Estimates of the dermal dose required to elicit an allergic response in sensitised individuals vary between from 0.09 and 12.5 $\mu\text{g}/\text{cm}^2$ (Scott and Proctor, 1997; Nethercott *et al.*, 1994).
255. Trivalent chromium may also act as a dermal sensitising agent but appears to be less potent in this respect than Cr(VI).
256. Respiratory sensitisation to Cr(VI) may also occur in response to workplace exposures (Keskinen *et al.*, 1980; Moller *et al.*, 1986) but is probably rare. There is no published information on the threshold concentrations of airborne chromium necessary to induce respiratory sensitisation or to provoke symptoms in those who are sensitised.
257. Chronic exposures to chromium fumes have been related to an excess of deaths from non-malignant respiratory disease in UK (Sorahan *et al.*, 1987; Davies *et al.*, 1991) and USA (Taylor, 1966) employees in the chromate production or electroplating industries. These associations are believed to relate directly to chromium exposures – rather than to confounding, current or past exposures to other metals such as nickel – but the effects of cigarette smoking have not been examined in detail. No reliable exposure estimates are available. In a chromate production plant in the USA at which atmospheric concentrations of Cr(VI) occasionally reached levels of 289 $\mu\text{g}/\text{m}^3$, high cumulative exposure was not associated with an increased risk of chronic bronchitis, emphysema, shortness of breath, or chronic cough (Pastides *et al.*, 1994). Among a group of chrome-plating workers in Sweden, with a median exposure of 2.5 years, transient reductions in lung volumes have been associated with

- exposures to Cr(VI) above $2 \mu\text{g}/\text{m}^3$ (Lindberg and Hedenstierna, 1983). Among 106 workers producing Cr(III) oxide and sulphate compounds – with estimated exposures to Cr(III) of $1.99 \text{ mg}/\text{m}^3$ there was no evidence of current respiratory disease (Korallus *et al.*, 1974). Two hundred and twenty one stainless steel production workers with median exposures to Cr(VI) of $0.0005 \mu\text{g}/\text{m}^3$ and to Cr(III) of $0.022 \mu\text{g}/\text{m}^3$ (similar to those in ambient air) had similar lung function and chest X-ray findings to an unexposed control group (Huvinen *et al.*, 1996).
258. Chronic rhinitis, nasal ulceration and perforation of the nasal septum have each been described in occupationally-exposed populations. There was a high incidence of these outcomes in an Italian population of chromate production workers with measured exposures to Cr(VI) of $10 \mu\text{g}/\text{m}^3$ (Sassi, 1956). In the Swedish chrome-platers described above, clinical evidence of nasal disease was evident among employees with mean exposure levels to Cr(VI) of $2\text{--}200 \mu\text{g}/\text{m}^3$. No significant nasal effects were observed in workers exposed at peak levels of $0.2\text{--}1 \mu\text{g}/\text{m}^3$. It is suggested that nasal adverse effects may in part be attributable to chromium salts being applied directly from contaminated fingers.
259. Sub-clinical evidence suggestive of renal damage has been described in some populations with occupational exposure to chromium compounds. In 43 men working in the chromate and dichromate production industry, where occupational exposures to Cr(VI) were between 50 and $1000 \mu\text{g}/\text{m}^3$ there were increased urinary levels of small proteins (retinol binding protein and tubular antigens) (Franchini and Mutti, 1988). Studies of populations with lower exposures have found equivocal or no adverse renal effects. Urinalysis of samples from Italian chromate production workers with estimated exposures of $10 \mu\text{g}/\text{m}^3$ found no abnormalities (Sassi, 1956). Elevated urinary levels of β 2-microglobulin were observed in chrome platers with personal exposures over about five years to Cr(VI) of $4 \mu\text{g}/\text{m}^3$ (Lindberg and Vesterberg, 1983; Liu *et al.*, 1998); but not in retired platers suggesting a reversible effect (Lindberg and Vesterberg, 1983). Occupational exposure to Cr(III) or Cr(0) does not appear to be associated with adverse renal effects.
260. In addition to allergic sensitisation, direct skin contact with chromium salts can give rise to irritant dermatitis and skin ulceration. These have been related to airborne concentrations of chromium in the workplace but it is difficult to disentangle these from dermal exposures.
261. High but unquantified exposures to Cr(VI) compounds have been reported to provoke ocular irritation, gastrointestinal ulceration, temporary neurological symptoms and reversible changes in liver function.

5.3.3 Genotoxicity

5.3.3.1 *in vitro* studies

262. There is a large body of in-vitro work describing genotoxic effects of Cr(VI) compounds in mammalian cells; studies of Cr(III) compounds on the other hand have been largely negative probably because they are less able to cross cell membranes (summarised in ATSDR, 2000).

5.3.3.2 Animal/bacterial studies

263. Alterations in pulmonary DNA, including chromosomal aberrations and sister chromatid exchanges, have been observed in rats after intratracheal exposure to Cr(VI) (Izzotti *et al.*, 1998); and in peripheral lymphocytes after exposure by inhalation to Cr(0). Similarly, gene mutations have been induced in fruit flies after exposure to Cr(VI) (ATSDR, 2000). Soluble Cr(VI), but probably not Cr(III), compounds are mutagenic in *Salmonella typhimurium* reverse mutation assays (ATSDR, 2000).

264. A number of occupational studies have reported increased frequencies of chromosomal aberration or sister chromatid exchange in workers exposed to Cr(VI) during chrome-plating or stainless steel welding (Sarto *et al.*, 1982; Stella *et al.*, 1982; Werfel *et al.*, 1998). These changes have not been related to Cr(VI) exposure and the effects of confounding genotoxic exposures have not been examined. Several similar studies have reported negative findings (Husgafvel-Pursianen *et al.*, 1982; Littorin *et al.*, 1983; Nagaya *et al.*, 1991).

5.3.4 Malignant effects

5.3.4.1 Animal studies

265. Chromium compounds have been reported to cause lung tumours in some experimental animals following inhalation (HSE, 2002). However, the literature is mixed with several studies in rats, rabbits and guinea pigs reporting little or no increase in tumour formation (Baetjer *et al.*, 1959; Steffee and Baetjer, 1965; Lee *et al.*, 1989). Based on their increased solubility and bioavailability, Cr(VI) compounds are generally agreed to be more carcinogenic than Cr(III) compounds (ICDA, 1997).

5.3.4.2 Human studies

266. There is a large body of evidence from the USA, Europe and the far East associating occupational exposure to chromium compounds with lung cancer, and, more rarely, nasopharyngeal cancer (ATSDR, 2000; Hayes, 1988; USEPA, 1998). The most consistent associations have been observed among workers in the chromate production and chromate pigment industries. Risks of lung cancer increase with the intensity and duration of exposure and the strength of association makes it unlikely that the results are due to uncontrolled confounding by cigarette smoking or

other factors. Studies of workers in the chrome plating industry have found less consistent associations and studies of workers engaged in stainless steel welding and ferrochrome alloy production have been inconclusive.

267. A review of the largest and best-designed studies of occupational lung cancer, to date, was published in 1996 (Steenland *et al.*, 1996). The information from these was used to estimate the range of excess deaths across five levels of exposure (SCOEL, 2004); the findings are summarised in Table 5.2.

Table 5.2: Estimated excess numbers of lung cancer deaths by exposure intensity to hexavalent chromium compounds.

Working-life exposure to various hexavalent chromium compounds	Excess number of deaths from lung cancer (range)
50 µg/m ³	5-28
25 µg/m ³	2-14
10 µg/m ³	1-6
5 µg/m ³	0.5-3
1 µg/m ³	0.1-0.6

268. Occupational exposures are generally to both Cr(III) and Cr(VI) with the possibility in some occupations of co-exposures to other substances such as nickel. Toxicological studies show that Cr(VI) is carcinogenic but that Cr(III) is less so, if at all (IARC, 1997). For this reason it is widely accepted that the increased risk of cancer in occupational studies is attributable to Cr(VI). It should be noted that Mancuso (1997) in a study of chromate workers in Ohio, concluded that cancer was also associated with exposure to Cr(III), but this conclusion has been questioned. In the leather tanning industry, where exposure is mainly to Cr(III), studies in the USA, UK and Germany have reported no increased risk of cancer.
269. There is a lack of informative studies of the effects of community exposures to airborne chromium. A single report of a study of the population living near a ferrochrome alloy plant in Sweden found no excess risk of lung cancer (Axelson and Rylander, 1980).
270. On the basis of the combined evidence from epidemiological and animal studies IARC (1997) classed Cr(VI) as 'carcinogenic to humans' (Group 1). The USA Environmental Protection Agency (USEPA) has classified Cr(VI) as Group A, 'a known carcinogen by inhalation'.
271. Further, IARC classified Cr(III) and metallic compounds as 'not classifiable as to their carcinogenicity to humans' (Group 3). This was based on inadequate evidence in humans and limited evidence in experimental animals.

5.3.5 Reproductive and developmental toxicity

272. An increase in the incidence of spontaneous abortions among the wives of stainless steel welders (exposed to chromium fume) has been reported in two Danish populations (Hjollund *et al.*, 2000; Bonde *et al.*, 1992) but not in a third (Hjollund *et al.*, 1995). None of these studies reported risks in relation to measurements of chromium exposure.
273. In comparison to an unexposed control group, higher numbers of morphologically abnormal sperm were found in a small study of employees of a factory manufacturing chromium sulphate in India (Kumar *et al.*, 2005). These changes were positively correlated with blood chromium levels. Similar findings have been reported among welders in India (Danadevi *et al.*, 2003) and among employees exposed to Cr(VI) in China (Li *et al.*, 2001); but not among welders in Denmark (Hjollund *et al.*, 1998). Again none of these studies reported measurements of chromium in air and the effects of confounding exposures cannot be discounted.
274. Two reports (in Russian) of women working in a dichromate manufacturing plant in Russia described increased rates of (undefined) complications during pregnancy and childbirth (Shmitova, 1980; Shmitova, 1978). It is not clear that these outcomes can be attributed to chromate exposure; no exposure measurements were reported. No increase in abnormal birth outcomes in relation to welding was found in a cohort of 10,000 Danish metalworkers (Bonde *et al.*, 1992).

5.4 Evaluations and recommendations by other organisations

275. Exposure to chromium in ambient air has been reviewed by the WHO, Defra and the Environment Agency (EA), the USEPA and the US Agency for Toxic Substances and Disease Registry (ATSDR). The UK Health and Safety Commission (HSC) and the American Conference of Governmental Industrial Hygienists (ACGIH) have published limits and guidelines on workplace exposures.
276. The WHO (2000) classifies Cr(VI) compounds as human carcinogens by inhalation exposure. They were unable to recommend an air quality guideline based on a safe level of exposure. A lifetime unit risk for lung cancer of 4×10^{-2} per $\mu\text{g}/\text{m}^3$ in air was derived by averaging the results of studies of four cohorts of chromate production workers (WHO, 2000). Extrapolation from this value by calculation equates excess lifetime risks of 1 in 10,000, 1 in 100,000 and 1 in 1,000,000 with exposures to concentrations of $2.5 \text{ ng}/\text{m}^3$, $0.25 \text{ ng}/\text{m}^3$ or $0.025 \text{ ng}/\text{m}^3$. The WHO note that only a proportion of the total concentration of chromium in air comprises Cr(VI) and that other forms of chromium are not carcinogenic.
277. The USEPA Reference Dose (RfD) for chronic oral exposure to Cr(III) is $1.5 \text{ mg}/\text{kg}$ body weight day per day based on a no observed adverse effect level (NOAEL) in a rat feeding study (USEPA, 1998). This is an estimate of a daily exposure by ingestion that is likely to be without an

- appreciable risk of deleterious effects during a lifetime. No inhalation reference concentration (RfC) is available for Cr(III). The US EPA RfD for noncancer effects arising from exposure to Cr(VI) is 3 µg/kg body weight day per day based on a NOAEL in a rat drinking water study (USEPA, 1998). The RfC for non-cancer effects arising from exposure to Cr(VI) in the form of chromic acid mists and dissolved Cr(VI) aerosols is 8 ng/m³ based on nasal septum atrophy in exposed workers. This is an estimate of an airborne concentration that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC for non-cancer effects arising from exposure to Cr(VI) as particulate is 100 ng/m³ based on the results of a 90 day study in rats. The confidence of the USEPA in their RfCs for chromic acid mists and Cr(VI) dusts are low and medium, respectively. The same agency has estimated the unit risk factor for lifetime (lung) cancer risk arising from exposure to Cr(VI) to be 1x10⁻² per µg/m³ in air. Concentrations of 8 ng/m³, 0.8 ng/m³ and 0.08 ng/m³ are extrapolated to increased life-time cancer risks of 1:10 000, 1:100 000 and 1:1 000 000, respectively (USEPA, 1998).
278. The USEPA and WHO unit risks are of very similar magnitude, in spite of being based on different occupational studies.
279. Defra and EA have not developed guidelines for inhalation exposures to chromium, but have set an inhalation Index Dose to minimise the risk of lung cancer arising from exposure to dust from chromium contaminated soils. An Index Dose for inhalation exposure of 0.001 µg/kg body weight/day was derived for Cr(VI) which represents “a risk level from possible exposure to a particular substance from a source” and is accompanied by an ALARP (as low as reasonable practicable) notation (also known as an inhalation Tolerable Daily Intake) (Defra and EA, 2002). This is based on the calculated concentration of Cr(VI) in air associated with a 10⁻⁴ lifetime cancer risk (ie 2.5 ng/m³) as determined by WHO (2000). An oral tolerable daily intake (TDI) for Cr(VI) of 3 µg/kg body weight/day was derived for children of six years or over and adults.
280. The US ATSDR (2000) derived an inhalation Minimal Risk Level (MRL) for Cr(VI) as chromium trioxide mist and other dissolved Cr(VI) aerosols and mists, of 5 ng/m³ for intermediate exposure (15-364 days). This was based on the development of upper respiratory effects in exposed workers. A separate MRL for intermediate exposure to particulate Cr(VI) compounds of 1 µg/m³ was derived based on the findings of a 90 day study in rats. The ATSDR believed it to be inappropriate to set a long term MRL for non-cancer effects because of the over-riding importance of cancer as a health endpoint.
281. The UK HSC has set a Workplace Exposure Limit (WEL) of 0.5 mg/m³ (8-hour time weighted average (TWA)) for chromium metal, Cr(II) compounds and Cr(III) compounds and a WEL of 0.05 mg/m³ (8-hour TWA) for Cr(VI) compounds (HSE, 2005). Workplace Exposure Limits are occupational exposure limits set under the Control of Substances Hazardous to Health

(COSHH) Regulations (2002 as amended). The WEL for Cr(VI) compounds was based on the lowest airborne concentrations that could be achieved by following good occupational hygiene practices across the majority of British industry. No safe level of exposure could be identified.

282. The ACGIH (2005) have set a Threshold Limit Value (TLV) for chromium metal and Cr(III) compounds of 0.5 mg/m^3 to protect against respiratory irritation and dermatitis. This is a level of exposure that has not been observed to cause adverse effects in the workplace. The TLV for water-soluble Cr(VI) compounds is 0.05 mg/m^3 and is intended to protect against liver and kidney toxicity and respiratory effects. This limit may be reviewed in the future. The TLV for insoluble Cr(VI) compounds is 0.01 mg/m^3 , based on workplace studies of cancer in humans and is intended to provide protection for respiratory effects and cancer. A TLV is a concentration to which nearly all workers may be repeatedly exposed over a working lifetime without adverse effects and the TLVs for chromium and chromium compounds have been set as 8-hour TWA's.
283. The US Occupational Safety and Health Administration (OSHA) has published a final standard for occupational exposure to Cr(VI) (OSHA, 2006). This standard reduced the earlier allowable exposure by a factor of ten. The permissible exposure limit (PEL) for Cr(VI), and for all its compounds, is $5 \text{ }\mu\text{g/m}^3$ air, as an 8-hour TWA.

5.5. Justification for air quality guideline

284. The Panel is setting an air quality guideline for Cr(VI) due to studies showing its toxicity. No guidelines are proposed for Cr(III) and Cr(0).
285. The most important effect for inhaled Cr(VI) for which there is adequate information on exposure and response appears to be the induction of lung cancer. There are insufficient human data on issues such as genotoxicity to know whether or not there is a threshold of exposure and whether or not the relationship between dose and risk (especially at low exposures) is linear or otherwise. The Panel is aware of considerable and currently unresolved controversy in these areas and has elected to adopt a precautionary approach. This may need to be reviewed if further information becomes available.
286. As far as is known, the exposures to chromium that are necessary to induce non-carcinogenic disease are greater than those that induce lung cancer.
287. The approach adopted here for guideline-setting is directly analogous to that used by EPAQS in setting standards for other chemical carcinogens such as benzene and polycyclic aromatic hydrocarbons.
288. New analyses including quantitative risk assessment of a cohort of chromate production workers in Baltimore have been reported (Gibb *et al.*, 2000; Park *et al.*, 2004). These concerned a cohort of 2,357 chromate production workers with 122 lung cancer deaths. Extensive records of

systematic air sampling which included total Cr(VI) were available for the cohort and smoking habit reported at hire was included in the modelling. On account of its size and exposure characterisation it is the most suitable for deriving a standard. Stratification by quintiles of number of deaths from lung cancer indicates a monotonic increase in risk of death with increasing cumulative exposure to Cr(VI), independent of smoking.

289. A statistically significant increase in standardised mortality from lung cancer was reported for employees in the lowest of the five categories of cumulative exposure (0.0000-0.0282 mg/m³.years). The mid point of this range is 0.0141 mg/m³.years which converts to an average annual concentration of 0.00035 mg/m³ (0.35 µg/m³) over a 40 year working lifetime. If this concentration is considered as a Lowest Observed Adverse Effect Level (LOAEL) then, following the precedent set in earlier reports by this Panel, division by a factor of ten, giving a concentration of 0.035 µg/m³, provides a notional NOAEL. This has further been divided by a factor of ten to allow for the greater exposure duration of the general public and a further factor of ten to allow for the presence of susceptible groups from within the general population. This leads to a guideline value of 0.35 ng/m³ of Cr(VI) as CrO₃.
290. The measurements made in this study were of 'Cr(VI) as CrO₃'. Expressed as Cr(VI) the guideline value above must be multiplied by a factor of 0.52, producing a figure of 0.2 ng/m³.

5.5.1 Sensitivity to method of derivation

291. Unit risk approach. There are three choices of exposure response for determining an acceptable level for public protection: 1) USEPA, based on the Ohio chromate production workers; 2) WHO based on a hybrid of Baltimore chromate production workers and Norwegian ferrochrome workers; and 3) Park *et al.* (2004) analysis of Baltimore chromate production workers. Our opinion is that we should use the last of these since it appears to use the best data and to be best analysed.
292. Park *et al.* (2004) estimated that 1mg/m³.year of cumulative exposure to Cr(VI) (as CrO₃) with a lag of five years had a relative rate of 2.44 (95% CI 1.54 to 3.83). This was used to estimate the unit risk for lung cancer per µg/m³ over a life-time using the formula in WHO (2000):
- UR = P₀ (RR-1)/life time exposure
 - P₀ = 0.04 (as in WHO 2000)
 - RR-1 per mg/m³ = 1.44 (from Park *et al.*, 2004)
 - Life-time average exposure = 8/24x240/365x1/70 = 0.003131
 - Unit risk = (0.04x1.44)/(8/24x240/365x1/70) = 18.40 per mg/m³
 - = 0.0184 per µg/m³ (1.8 x 10⁻²)
293. This is close to the unit risks estimated by the USEPA from different data, and WHO using a combination of Baltimore and Norwegian data (see earlier).

294. The risks of lung cancer associated with life-time exposures to different levels are: $0.05 \text{ ng/m}^3 = 1 \text{ in } 10^{-6}$ ($10^{-6}/1.84 \times 10^{-5}$); $0.5 \text{ ng/m}^3 = 1 \text{ in } 10^{-5}$; $5.0 \text{ ng/m}^3 = 1 \text{ in } 10^{-4}$.
295. The guideline value of 0.35 ng/m^3 as CrO_3 derived using the customary EPAQS method above equates to a lifetime risk of 7 in one million people. This gives confidence that the EPAQS procedure yields a guideline value consistent with that that would be generated by other procedures such as the unit risk method.
296. At current upper UK urban levels of chromium of around 15 ng/m^3 containing an estimated 4 ng/m^3 of Cr(VI) , the increased risk of lung cancer would amount to a little under 1 in 10,000 which is comparable to the rate of death from lung cancer in non-smokers derived from a 20 year follow-up of male British doctors.
297. Particulate material may be more potent as any effect may be extended in time and effectively localised. However, particulate material will be largely Cr(III) and a standard must take account of this.

5.6. Recommendation

0.2 ng/m^3 chromium in the Cr(VI) oxidation state in the PM_{10} size fraction as an annual mean.

- 298. The Panel believes that the recommended guideline for Cr(VI) should offer a high level of protection against the risk of lung cancer and of other adverse health effects. However, for this as for other carcinogens, the Panel advocates a progressive reduction in airborne concentrations below this guideline.**

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ALARP	As low as reasonably practicable
As	Arsenic
ATSDR	US Agency for Toxic Substances and Disease Registry
BAT	Best Available Techniques
Be	Beryllium
CBD	Chronic Beryllium Disease
Cr	Chromium
COPD	Chronic Obstructive Pulmonary Disease
COSHH	Control of Substances Hazardous to Health
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment
Defra	Department for Environment, Food and Rural Affairs
DMA	Dimethylarsinic acid
EALs	Environmental Assessment Levels
EA	Environment Agency
EC	European Commission
EEB	European Environment Bureau
EPA	US Environmental Protection Agency
EPAQS	Expert Panel on Air Quality Standards
HSC	Health and Safety Commission
HSE	Health and Safety Executive
g	Gram
IPCS	International Programme on Chemical Safety.
LOAEL	Lowest Observed Adverse Effects Level
m ³	Cubic metre (equivalent to 1000 litres)
µg	Microgram (one millionth of a gram)
µm	Micrometer (one millionth of a metre)
µg/m ³	Micrograms per cubic metre
MEL	Maximum Exposure Limit
mg	Milligram (one thousandth of a gram)
MMA	Monomethylarsonic acid
MRL	Minimal Risk Level
ng	Nanogram (one billionth of a gram)
Ni	Nickel
NOAEL	No Observed Adverse Effects Level
NPL	National Physical Laboratory
OEL	Occupational Exposure Limit
OSHA	USA Occupational Safety and Health Administration
PAH	Polycyclic Aromatic Hydrocarbons
PEL	Permissible Exposure Limit
RfC	Reference Concentration
RfD	Reference Dose
SMR	Standardised Mortality Ratio
TDI	Tolerable daily intake
TLV	Threshold Limit Value
TLV-TWA	Threshold Limit Value-Time Weighted Average
TWA	Time Weighted Average
USDHHS	US Department of Health and Human Services

WEL	Workplace Exposure Limits
WHO	World Health Organisation

Glossary

Acute toxicity / effects	Adverse effects occurring within a short time after receiving a single dose of a chemical or immediately following short or continuous exposure, or multiple doses over 24 hours or less.
Adenoma	A benign tumour with the structure or appearance of a gland or originating in a gland.
Adenosine diphosphate (ADP)	Formed following hydrolysis of adenosine triphosphate (ATP).
Adenosine triphosphate (ATP)	A nucleotide that is of fundamental importance as a carrier of chemical energy in all living organisms.
Antioxidant	A substance that inhibits oxidation and can guard the body from the damaging effects of free radicals.
Anthropogenic	Man-made.
Atherosclerosis	A disease affecting arterial blood vessels. It is a chronic inflammatory response in the walls of arteries, commonly referred to as a 'hardening' or 'furring' of the arteries.
Best Available Technique (BAT)	The most effective and advanced technique for the prevention, or where that is not practicable, the minimisation of emissions and impact on the environment as a whole, taking into account the availability of the technique for the type of process concerned and cost.
Berylliosis or chronic beryllium disease (CBD)	An occupational lung disease arising from an allergic-type response to beryllium and its compounds in the workplace. The condition is characterised by lung scarring and is incurable, treatment being symptomatic only.
Carcinoma	A malignant tumour or a cancer.
Carcinogen	A substance or agent that produces cancer.
Carcinogenic	Cancer producing.
Chronic obstructive pulmonary disease (COPD)	A group of diseases characterised by pathological limitation of airflow in the airway that is not fully reversible. COPD is an umbrella term for chronic bronchitis, emphysema and a range of similar lung disorders.

Chronic toxicity / effects	Adverse effects occurring as a result of multiple exposures to a chemical over an extended period of time or a significant fraction of the animal's or the individual's lifetime (usually more than 50%).
Clastogenicity	Chromosomal breakage.
Conjunctivitis	Inflammation of the conjunctiva, the mucous membrane which lines the inner surface of the eyelids and is reflected over the front of the eye-ball.
Cytoplasm	The material surrounding the nucleus of a cell.
Deoxyribose nucleic acid (DNA)	The material inside the nucleus of cells that carries genetic information.
Dermatitis	Inflammation of the skin.
Dyspnoea	Shortage of breath.
Emphysema	A pathological enlargement of the air vesicles of the lungs.
Encephalopathy	Disease of the brain in general.
Environmental Assessment level (EAL)	Benchmarks in a particular environmental media which denote the concentration of a chemical that should have no adverse effects on the natural environment or human health. By comparison with the predicted environmental concentrations arising from releases, they are intended to enable the significance of releases to be assessed, the need for further pathway modelling to be determined and the relative impact of pollutants released to different environmental media to be compared.
Epidemiology	Study of the distribution of disease among populations; and of the causes of this distribution.
Epithelium	The tissue that covers the external surface of the body and lines hollow structures.
Ferritin	A water-soluble crystalline protein containing ferric iron that occurs in many animals, especially in the liver and spleen, and is involved in the storage of iron by the body.

Gastrointestinal tract	The system of organs within multicellular animals that takes in food, digests it to extract energy and nutrients, and expels the remaining waste. It includes the mouth, pharynx, oesophagus, stomach, intestines and anus.
Genotoxic carcinogen	Known to cause cancer as a result of interacting with DNA.
Granuloma (plural granulomata)	Small nodule.
Health and Safety Commission (HSC)	The Health and Safety Commission's remit is to protect everyone in Great Britain against risks to health or safety arising out of work activities; to conduct and sponsor research; promote training; provide an information and advisory service; and submit proposals for new or revised regulations and approved codes of practice.
Health and Safety Executive (HSE)	Britain's Health and Safety Commission and Health and Safety Executive are responsible for the regulation of almost all the risks to health and safety arising from work activity in Britain.
Histological	Concerned with the minute structure of the tissues of animals.
Hypercalcaemia	Elevated calcium levels in the blood.
Hypercalciuria	Condition of elevated calcium in the urine.
Hyperkeratosis	Excessive development of the horny layer of the skin.
Hyperpigmentation	Excessive pigmentation.
Hypersensitivity	Increased or abnormal sensitivity to compounds which can trigger a specific immune response accompanied by tissue damage.
Hypertension	Abnormally high blood pressure
Hypermethylation	Excessive addition of methyl groups.
Hypomethylation	Insufficient addition of methyl groups.
Intratracheal	Within the trachea or windpipe.
Leucocytes	A colourless corpuscle, eg, one of the white blood-corpuscles, or one of those found in lymph, connective tissue, etc.

Lowest observed adverse effects level (LOAEL)	The lowest level of exposure at which a statistically significant increase in the frequency of an adverse health effect has been observed in a study.
Lymph	A colourless liquid found within the lymphatic system, into which it drains from the spaces between cells.
Lymphocyte	A type of small leucocyte which has a single round nucleus and little or no granulation in the cytoplasm, constitutes about a quarter of the total leucocytes in the blood stream, is found in large numbers in the lymph nodes and other lymphoid tissue, and is a major agent in most immunological processes.
Lymph nodes	A mass of lymphoid tissue, many of which occur at intervals along the lymphatic system. Lymph in the lymphatic vessels flows through the lymph nodes which filter out bacteria and other foreign particles so preventing them from entering the bloodstream and causing infection.
Messenger RNA (mRNA)	Responsible for carrying the genetic code transcribed from DNA to specialised sites within the cell known as ribosomes, where the information is translated into protein composition.
Metalloid	An element which is intermediate of metals and nonmetals in terms of malleability, ductility, conductivity and lustre.
Mucocilliary transport	The normal system of removal of particles from the airways of the lung using the combination of microscopic motile protrusions on the surface of airway cells ('cilia') and mucous produced by airway glands.
Mutagenic	Changes the structure of genetic material.
Nasopharyngeal	Of or relating to the nose and the pharynx jointly, or the nasopharynx, which is the uppermost part of the pharynx, lying above the soft palate and connecting with the nasal cavity.
No observed adverse effect level (NOAEL)	A highest exposure level at which there is no statistically or biologically significant increase in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse, nor precursors to adverse effects.

Occupational Exposure Limit (OEL)	The UK Health and Safety Commission sets occupational exposure limits which are concentrations of substances in the air at or below which occupational exposure is considered to be adequate.
Oedema	Excessive accumulation of fluid in the body tissues. When fluid accumulates in the lung it is known as a pulmonary oedema.
Oncogene	A gene whose products may in certain circumstances transform a cell containing them into a tumour cell.
Oxidation state	A measure of the electron control that an atom has in a compound compared to the atom in the pure state.
Oxidative phosphorylation	A metabolic pathway that uses energy released by the oxidation of nutrients to produce adenosine triphosphate (ATP).
Peripheral neuropathy	Neuropathy (disease or dysfunction of the nervous system) affecting one or more peripheral nerves, causing sensory changes and motor weakness.
Pharmacokinetics	Branch of pharmacology dedicated to the determination of the fate of substances administered externally to a living organism.
Pulmonary	Relating to the lung
Pulmonary fibrosis	Chronic progressive interstitial lung disease of unknown origin, characterised by an abnormal and excessive deposition of fibrotic tissue in the pulmonary interstitium with minimal associated inflammation.
Pulmonary interstitium	The part of the lungs which lies between the principal cells, tissues, etc.
Pulmonary oedema	Build up of fluid in the lungs causing breathlessness.
Raynaud's phenomenon	Spasm of the arteries of the digits (often due to low temperature or vibration) leads to pallor, pain, and numbness, and in severe cases to gangrene.
Respiratory tract	The organs that are involved in breathing. These include the nose, throat, larynx, trachea, bronchi and lungs.
Renal stones	Kidney stones

Ribonucleic acid (RNA)	A complex organic compound in living cells concerned with protein synthesis.
Sarcoidosis	A chronic disease characterised by the widespread appearance of sarcoid granulomata in the lungs and other tissues. Its cause is usually unknown but it can mimic berylliosis.
Subcutaneous	Lying or situated under the skin.
Threshold Limit Values (TLVs)	These values are established by the American Conference of Governmental Industrial Hygienists (ACGIH). They are the concentration in air of a substance to which, it is believed that, most workers can be exposed daily without adverse effect. Quoted as time weighted concentrations for a seven or eight hour workday and a 40 hour working week. For most substances the value may be exceeded, to a certain extent, provided there are compensating periods of exposure below the value during the workday or, in some cases, working week. A limited number of substances are given ceiling concentrations that should never be exceeded.
Toxicological	Relating to toxicology, ie, the nature and effects of poisons.
Toxicokinetics	Application of pharmacokinetics to determine the relationship between the systemic exposure of a compound in experimental animals and its toxicity. It is used primarily for establishing relationships between exposures in toxicology experiments in animals and the corresponding exposures in humans.
Transferrin	Any of several beta globulins found in blood serum which bind and transport iron.
Vasospastic symptoms	Sudden constriction of a blood vessel, resulting in reduced flow.

Appendix 1

Setting air quality standards and guidelines for chemical carcinogens

A1 Introduction

299. One of the generic problems for an expert committee in setting air quality standards and guidelines for the protection of human health is that it has to work from pre-existing data, which are usually far from ideal; rarely is it possible to commission studies specifically to aid in the standard-setting process. The pre-existing data usually fits into one of three categories:

- Studies in which human subjects have been administered controlled exposures of pollutants in a clinical setting and their response closely monitored (termed chamber or challenge studies);
- Epidemiological studies of human populations either in the workplace or the non-occupational environment;
- Studies using animals as model species.

300. In the case of chemical carcinogens, the first type of data are unavailable for ethical reasons and the epidemiological data, when relating to specific chemical substances as opposed to the air pollutant mix as a whole, are derived from exposures in the workplace. The concentrations there are often higher by several orders of magnitude than those to which the general public are exposed in their everyday lives. As a last resort, expert panels have to base their judgements on studies with animal models, but there is always a problem of how to extrapolate that information between species. This is particularly problematic when a chemical proves carcinogenic in one test species but not in another. In the case of the chemical carcinogens addressed by EPAQS thus far (benzene, 1,3-butadiene and polycyclic aromatic hydrocarbons), there have generally been high quality studies of cancer incidence in occupationally exposed workers (albeit relatively few in number). It is these studies that have formed the basis for standard-setting. The approach adopted thus far by EPAQS has differed from that used by the World Health Organisation (WHO) and some other countries. The purpose of this appendix is to explain the EPAQS approach and to compare and contrast it with the other main approach used, that based upon quantitative risk assessment.

301. Before describing the approaches used, it is important to distinguish between genotoxic and non-genotoxic carcinogens. The former act by damaging DNA in the nucleus of the cell. In this case, a single molecule of the chemical carcinogen *could* lead to cancer, but the chances are exceedingly small. However, because of this there is no level of exposure which is entirely without risk. Non-genotoxic carcinogens act by other mechanisms, such as by damaging tissue, leading to continuous re-

growth during which cell mutations may occur, leading in turn to cancer. For non-genotoxic carcinogens, there may be a threshold, or safe level of exposure below which the processes preceding carcinogenesis do not take place, and hence cancer does not result. Benzene, 1,3-butadiene and polycyclic aromatic hydrocarbons are believed to be, and are generally accepted as, genotoxic carcinogens. The evidence relating to the metals in this report is less clear, but consistent with the Panel's precautionary approach, a genotoxic mechanism has been assumed. The following discussion relates to genotoxic carcinogens.

A2 The EPAQS approach to setting air quality guidelines for chemical carcinogens

302. EPAQS first developed its approach when recommending an air quality standard for benzene. This is a chemical to which there had been widespread exposures in industry. There was a well known excess of leukaemia in the synthetic rubber industry attributable to benzene exposure. The approach of EPAQS was to review the occupational exposure literature and to identify a high quality study in which the excess cases of cancer in large groups of workers with different exposures to benzene had been estimated. Generally, as expected, those workers with the largest integrated exposures to benzene were found to have the highest risk of contracting cancer. By examining the less exposed groups of workers it was possible to identify the highest exposure concentration at which no significant excess of cancers could be identified. It was accepted that had larger numbers been studied then an effect might have been discovered. Thus no completely safe level of exposure could be identified. However, the Panel took as a starting point a figure derived from the published studies that showed no effect (EPAQS, 1994).
303. Having identified a starting point from a study of workers in a synthetic rubber plant in North America, EPAQS went about building in safety margins to protect the general public. They built in two factors as follows:
- a factor to take account of the fact that the general public is exposed to polluted air for 24 hours a day, 365 days a year for a lifetime (taken as 70 years) whilst the occupationally-exposed worker will be exposed only for about 220 working days per year, 40 hours per week for a 40 year maximum working lifetime. This led to an exposure duration safety factor of ten;
 - a second safety factor of ten was also applied to recognise the fact that those exposed in industry are generally healthy adult workers whereas the general public includes the very young and the infirm who may, perhaps for genetic reasons, be more vulnerable to developing cancer as a result of exposure to carcinogens.
304. The combination of the two safety factors leads to an overall factor of 100 by which the starting figure is divided to give a guideline value at which, in the judgement of the Panel, the risks to the general public from benzene

exposure should be exceedingly small. The standard arrived at was 5 ppb (annual average concentration). The panel recognised that this was greater than the current ambient concentration and proposed as a target 1 ppb. No formal mechanism for deriving 1 ppb from 5 ppb was proposed. Outdoor benzene exposures in the UK are nowadays generally around 1 part per billion, or less, compared to part-per-million exposure levels for the workers in tyre manufacture who contracted leukaemia.

305. When EPAQS examined occupational cancer data resulting from exposure to polycyclic aromatic hydrocarbons, the Panel found that even the least exposed group of workers in an aluminium smelter experienced a small but significant increase in lung cancer incidence. The studies did not report a No observed adverse effect level (NOAEL). The lowest category of exposures at which an effect on cancer was seen was presented as a range and EPAQS took the lower boundary of that range and referred to it as a Lowest Observed Adverse Effect Level (LOAEL). Recognising that this still represented a small but significant risk of additional cancers, EPAQS divided the LOAEL by ten to reach a notional NOAEL to which additional safety factors, each of ten for duration of exposure and vulnerable groups were applied in order to reach a guideline.
306. In effect, therefore, the EPAQS approach identifies an amount of chemical carcinogen which is associated with minimal risk to those occupationally exposed. It then converts this to a lower concentration corresponding to that at which the general public would receive the same overall dose as those exposed occupationally over a working lifetime and then further applies a safety factor of ten to allow for vulnerable groups in the population. This approach is both logical and transparent but differs from that used by the WHO and some other countries.

A3 The quantitative risk assessment approach

307. The data from occupational exposures to chemical carcinogens tell us that at a certain (high) exposure concentration there is a particular level of additional risk for exposed workers. The quantitative risk assessment approach seeks to extrapolate the occupational data to lower concentrations and therefore to quantify the additional risk of cancer at environmentally meaningful concentrations. There are many ways in which this extrapolation can be made depending upon the assumed mechanism of carcinogenesis. This can lead to very different estimates of risk at low exposure concentrations, which is one of the weaknesses of the Quantitative Risk Assessment approach. In practice the simplest assumption and that used by the WHO is that the risk of cancer is zero only at zero concentration of that compound and increases proportionately with concentration. This is referred to as a linear model without threshold (i.e. there is no level below which no effect is thought to occur).
308. This method leads to an estimate of risk referred to as the incremental unit risk estimate which is defined by WHO as “the additional lifetime cancer

risk occurring in a hypothetical population in which all individuals are exposed continuously from birth throughout their lifetimes to a concentration of $1 \mu\text{g}/\text{m}^3$ of the agent in the air they breathe”.

309. The WHO is frank about the limitations to this approach (WHO, 2000) and one of its concerns shared by the Department of Health’s Committee on Carcinogenicity is that the method can give a spurious impression of precision when extrapolating data which already have inherent uncertainties over orders of magnitude in concentration. The WHO (2000) point out that the quantitative risk estimates should not be regarded as being equivalent to the true cancer risk, but to represent plausible upper bounds which may vary widely according to the assumptions on which they are based. Nonetheless, the method is very widely used and, for example, for benzene, yields an excess lifetime risk of leukaemia at an air concentration of $1 \mu\text{g}/\text{m}^3$ of 6×10^{-6} (WHO, 2000) – i.e. 6 in 1 million, meaning that six people in every million exposed to benzene at that concentration will develop leukaemia in a lifetime. The WHO does not directly utilise this unit risk factor to recommend a numerical air quality guideline but calculates the concentrations of airborne benzene associated with particular levels of excess lifetime risk. In the case of benzene, the excess lifetime risk of one in 10,000 occurs at a concentration of $17 \mu\text{g}/\text{m}^3$, a lifetime risk of one in 100,000 at $1.7 \mu\text{g}/\text{m}^3$ and a lifetime risk of one in 1 million at $0.17 \mu\text{g}/\text{m}^3$.
310. The quantitative risk assessment method uses the same occupational cancer data as a starting point and inherently very similar assumptions to the EPAQS method. However, unlike the EPAQS method it does not arrive at a single concentration as a guideline. Rather, it is necessary for the standard setting agency to specify a maximum tolerable level of risk which can then be converted to a guideline concentration using the unit risk factor. Governments have traditionally been reluctant to specify such levels of tolerable risk. To do so involves societal judgements, and arguably expert committees should not usurp the rights of society to make such judgements themselves.

A4 How do the methods compare?

311. As pointed out above, the starting points to the two methods are essentially identical although it may be easier for the unit risk factor method to take account of multiple sources of data which can be combined using standard meta-analysis methods. On the other hand, the EPAQS method allows the Panel to use as its starting point the study showing the greatest impact, in order to take a precautionary approach. The assumptions inherent in each method are also broadly similar in assuming linearity (proportionality) of response and no threshold. If one takes the standards recommended by EPAQS for benzene and polycyclic aromatic hydrocarbons, and converts them to an implied level of excess risk using WHO unit risk factors, the level of risk turns out to be about one in 100,000 lifetime risk .

A5 The specific case of Arsenic

312. In recommending an air quality guideline for arsenic, the Panel has adopted the procedure used previously by EPAQS in recommending standards for chemical carcinogens. Three studies were available from metal smelters and the lowest range of cumulative exposure that was associated with a statistically significant increase in lung cancer risk was less than 250 $\mu\text{g}/\text{m}^3\cdot\text{years}$ in a Swedish workforce and less than 833 $\mu\text{g}/\text{m}^3\cdot\text{years}$ and 750-2000 $\mu\text{g}/\text{m}^3\cdot\text{years}$ in two US workforces. The Panel adopted a precautionary approach and took the lowest exposures, corresponding to the Swedish workforce and took the mid-point of the exposure range whose lower bound was not defined in the study and was assumed to be zero. Thus, the mid-point was 125 $\mu\text{g}/\text{m}^3\cdot\text{years}$, which taking the precautionary assumption that those contracting cancer had been exposed for 40 year converts to an average concentration of 3 $\mu\text{g}/\text{m}^3$ over a 40 year working lifetime.
313. This yields 3 $\mu\text{g}/\text{m}^3$ as a LOAEL, and following the earlier practice of dividing by ten, 0.3 $\mu\text{g}/\text{m}^3$ (or 300 ng/m^3) as a NOAEL. Dividing by two further factors of ten, one to allow for exposure duration and the other for susceptible groups results in a recommended guideline value of 3 ng/m^3 .
314. The most recent quantitative risk evaluations of the workforce cancer data for arsenic yield pooled estimates of the unit risk of 1.43×10^{-3} per $\mu\text{g}/\text{m}^3$ (Viren and Silvers, 1994) and 1.5×10^{-3} per $\mu\text{g}/\text{m}^3$ (WHO, 2000). If one takes the figure from WHO (2000), then the EPAQS recommendation of 3 ng/m^3 equates to a lifetime risk of 4.5 in a million or about half of the one in 100,000 risk level discussed above as being of the order sometimes used in regulatory toxicology.

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