Medical Research Council

Institute for Environment and Health

IEH report on

HEALTH EFFECTS OF WASTE COMBUSTION PRODUCTS

1997 REPORT R7

The Institute for Environment and Health was established by the Medical Research Council at the University of Leicester in 1993. The Institute is partly funded by the Department of the Environment, the Department of Health and other Government Departments and Agencies by way of specific research and consultancy contracts.

This report incorporates the output of a workshop held in January 1996, and has been prepared by staff of the Institute for Environment and Health. The Institute gratefully acknowledges the contribution of our collaborators at the Institute of Public and Environmental Health, University of Birmingham, and all those who attended the workshop and provided material for inclusion in the Report.

The work involved in producing this report was carried out under contract as part of the New and Renewable Energy programme, managed by the Energy Technology Support Unit (ETSU) on behalf of the Department of Trade and Industry. The views and judgements expressed in this report are those of the Institute for Environment and Health and do not necessarily reflect those of ETSU or the Department of Trade and Industry, nor of the individual scientists who provided material or attended the workshop.

Principal authors: Charles Humfrey, Mark Taylor and Kwame Amaning

Additional text and scientific editing: Sarah Badley, Paul Harrison, Len Levy and Linda Shuker

Workshop chairman: Len Levy

Published by the Institute for Environment and Health, 1997

Printed by Page Bros, Norwich

ISBN 1 899110 09 7

Institute for Environment and Health
University of Leicester
94 Regent Road
Leicester LE1 7DD
UK

Contents

Executive summary

The purpose of this report is to provide information about the health effects of pollutants released during incineration processes to those responsible for making decisions on waste management and other interested parties. It also reviews and assesses the evidence for adverse health effects in epidemiological studies of incinerator workers and individuals living near incinerators. It takes account of the uncertainties surrounding some of these issues and makes recommendations for further studies on exposure and health effects. In conjunction with other information such as exposure data and details of exposed populations, the report should also aid in site-specific risk assessments.

Municipal solid waste (MSW) incinerators have been operating under modern pollution abatement standards for only a comparatively short period, so contemporary data on specific emissions and exposures are sparse. This report therefore relies heavily on published data for older incinerators, which tended to have lower standards of emission control.

The first phase of this study generated a list of pollutants known to be produced by the incineration of various types of waste. This list was too long for every chemical to be studied in detail, so the pollutants were ranked according to their effects on human health and the amounts likely to be released.

The ten pollutants considered to be the most important were then evaluated in detail. The report does not try to distinguish the relative importance of these chemicals, since the amounts of each emitted will vary from one incinerator to another.

The ten selected pollutants comprise five metals: cadmium, mercury, chromium, arsenic and nickel; three groups of organic compounds: dioxins (PCDD/Fs), polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs); sulphur dioxide (SO_2); and fine particulate matter (PM_{10}). Literature searches provided the most up-to-date information about the health effects of these pollutants, especially at low levels of exposure (where available) and these data were then reviewed.

HEALTH EFFECTS OF SELECTED POLLUTANTS

Most of the health data in the published literature relate to occupational or accidental exposure, and generally therefore to higher levels of exposure than those expected from waste incineration. There are few published studies on low-level exposure, and very few on the effects of exposure to mixtures of chemicals. Most studies concern exposure to a single chemical or a single group of chemicals (e.g. PCDD/Fs, PCBs, PAHs).

The health effects reported herein are not specific to incinerator emissions; they are the health effects of the individual chemicals, regardless of exposure source, as reported in the literature.

Many of the ten pollutants are considered to be carcinogenic, based on either animal studies or epidemiological studies, generally of people exposed at work or in accidents. Evidence that these chemicals cause cancer at environmental levels, however, is either absent or equivocal.

For other health effects there is evidence that some pollutants produce subtle damage at relatively low levels of exposure. For example, there have been reports that SO_2 and PM_{10} show dose-dependent effects on morbidity and mortality at background levels of exposure, particularly in susceptible people.

Generally, however, data on the effects of low-level exposure to these pollutants, either singly or in combination, is lacking. Moreover, all the pollutants considered are already present in the environment and it is difficult to assess what effect, if any, a small additional exposure resulting from incinerator emissions may have.

Cadmium

Occupational exposure to cadmium has been associated with an increased risk of lung cancer and a number of non-carcinogenic effects, including effects on the lungs (emphysema) and kidneys. The threshold for renal effects has been shown to be above current UK occupational exposure limits, although evidence of changes in kidney function has been found in some highly exposed people such as those living near zinc smelters. The implications of these effects for people living around incinerators and the general population are not clear. Nonetheless the contribution of incinerator emissions to background exposure is likely to be small.

Mercury

For mercury, the key health effects at low levels of exposure are renal damage and subtle behavioural effects. Urinary thresholds for mercury excretion and associated exposure levels in air have been proposed for both nephrotoxicity and behavioural effects. The significance of these effects with respect to the general population is unclear. Again, however, incinerator emissions are likely to have a very small effect on general background levels.

Arsenic

Inorganic arsenic causes both acute and chronic toxicity in a number of organs including the respiratory tract, skin, liver and peripheral nervous system. However, arsenic's most serious toxic property is carcinogenicity. This may follow ingestion or inhalation, the main target organs being the skin and the lungs, but these effects have only been demonstrated at relatively high occupational exposures and not at levels likely to be encountered in the environment.

Chromium

Occupational exposure to relatively high levels of hexavalent chromium causes damage to the nasal septum, dermatitis and lung cancer. Trivalent chromium is in general far less toxic and is not considered to be a carcinogen. Current occupational exposure limits for hexavalent chromium protect against nasal damage, and personal hygiene (skin care) protects against dermatitis. At much lower environmental exposure levels the most serious health outcome to be considered is lung cancer, for which a small risk cannot be excluded.

Nickel

Nickel can cause respiratory, gastrointestinal and renal effects, but the health effect of most concern is the carcinogenicity of inorganic nickel compounds. The cancer risk resulting from environmental exposure to these compounds is likely to be very small. Allergic sensitisation, particularly contact dermatitis, to nickel and its salts is also a recognised problem. This affects people who work with nickel and some people who wear jewellery containing nickel.

Dioxins

Exposure to dioxins at high doses can produce chloracne, and may adversely affect human metabolism, development and reproductive biology. These effects have been reported at exposure levels within one order of magnitude of the average background level or body burden, but there is a great deal of uncertainty. Current evidence suggests that dioxins may present a cancer hazard to humans, but this is by no means conclusive.

PAHs

Epidemiological evidence indicates elevated risks for lung, skin, and perhaps bladder and gastrointestinal cancers in certain groups of people exposed to mixtures containing PAHs, such as coke-oven workers and tobacco smokers. Animal experiments on individual PAHs have shown some to be carcinogenic, and the International Agency for Research on Cancer (IARC) has classified a number of PAHs as probably carcinogenic to humans. Owing to the variation in composition and concentration of individual compounds in PAH mixtures, the general risk of cancer resulting from environmental exposure is not possible to quantify.

PCBs

Information on the health effects of PCBs has come mainly from people exposed through heavy PCB contamination of their food. Few adverse effects have been definitely associated with low-level long-term exposure. Subtle developmental and reproductive effects in children exposed before birth or through breastfeeding have been reported at exposure levels of the same order of magnitude as those currently reported in the UK. At the moment there is not enough evidence to conclude that PCBs cause cancer in humans; the current concern over human exposure to PCBs is due to their undoubted toxicity in animals and their persistence in human tissues.

Particles (PM_{10})

Exposure to PM_{10} particles is associated with both acute and chronic health effects and increased mortality from a variety of causes in the general population, particularly in susceptible subgroups. These effects are dose-dependent and do not

appear to have a threshold. As with other pollutants the contribution to background levels from incinerator emissions is expected to be small.

Sulphur dioxide

Short-term occupational exposure to high levels of SO_2 irritates the upper respiratory tract. Both occupational and environmental exposure levels can produce bronchial constriction in sensitive subjects. Epidemiological studies have shown that long-term environmental exposure is associated with increased cardiorespiratory morbidity and mortality. Ambient exposure may also increase sensitisation to environmental allergens.

HEALTH EFFECTS IN POPULATIONS AROUND INCINERATORS

Epidemiological studies of people who work at or live near incinerators have shown no consistent excess incidence of any specific disease. Many of these studies, however, have not been able to detect adverse health effects reliably, either because they were too small in size or could not adequately account for confounding factors. Indeed, even the largest study, which investigated cancer incidence in over 14 million people living near MSW incinerators in the UK between the years 1974 and 1987 and found an excess of some cancers, reported that the most likely explanation for these observations was confounding by socio-economic factors.

With the implementation of the Environment Agency's Integrated Pollution Control regulations at the end of 1996, atmospheric releases of many of the pollutants considered in this report are controlled more tightly. As a result of this, exposure to all pollutants released from MSW incinerators will fall.

CONCLUSIONS AND RECOMMENDATIONS

In general, few data are available on the human health effects associated with low levels of exposure to the individual pollutants considered in this report; most of the information originated from either environmental accidents or occupational studies in which exposures have been generally much higher. Also, while many of the ten pollutants are considered to be carcinogenic, this is based on studies on

relatively highly exposed human populations or animal investigations. The epidemiological evidence that these substances represent a cancer risk at much lower environmental levels either does not exist or is equivocal.

For effects other than cancer, some of the pollutants have been shown individually to have effects at low levels of exposure. For example, SO_2 and PM_{10} are reported to cause dose–dependent increases in both morbidity and mortality in the general population. Generally however, data on the effects of background environmental exposures to combinations of chemicals are absent, making it difficult to assess any health impact resulting from relatively small additional exposures from incinerators. Thus, there is a clear need for further and better quality human exposure data for the pollutants considered here, particularly in populations living near incinerators.

No consistent pattern of ill-health has emerged from studies of incinerator workers or populations living near incinerators. Any future epidemiological studies investigating the health effects associated with living near incinerators should be designed so that small increases in risk can be detected, and should also adequately account for the various confounding or modifying factors.

1 General introduction

BACKGROUND

Every year the UK disposes of approximately 25 Mt of household and commercial wastes, collectively known as municipal solid waste (MSW), together with a similar quantity of waste from industry and smaller quantities of specialised wastes including solvents, scrap tyres and hospital waste. Currently most waste is buried in landfill sites with little or no energy recovery.

Even with available technology, however, there is much scope for exploiting waste as a resource. It has been estimated that if the energy content of the UK's waste were recovered by combustion it could produce nearly 4000 MW of electricity. Energy from waste (EfW) technologies, including MSW incineration, are potentially one of the most promising and economically attractive sources of renewable energy for the UK. Indeed, a report by the Royal Commission on Environmental Pollution published in 1993 stated that incineration is the best practicable environmental option for managing waste (RCEP, 1993). Extracting energy from waste also offers the benefits of reducing fossil fuel consumption and minimising the problem of methane emissions from landfill sites.

As a result of stricter environmental controls and the development of strategies for integrated waste management there is considerable interest in EfW technologies. There are, however, a number of potential barriers to the deployment of modern MSW-to-energy schemes. Key amongst these is the general public concern that any large-scale incineration process will give rise to combustion products with hazardous effects on human health.

For this and other reasons, one of the objectives of the Department of Trade and Industry's EfW programme is to provide information and guidance on the environmental costs and benefits of the technology to developers, local authorities and others involved in EfW projects. The current study falls under this heading.

OBJECTIVES

Possible health effects have proved to be a key concern in the debate over strategies involving waste combustion. For any source of emissions there is a requirement to investigate and define the composition, quantities and toxic properties of the emissions. The toxicology and epidemiology of the health effects of the products of waste combustion are both complex and uncertain.

Waste incineration can give rise to a wide range of gases and aerosols, including fine particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}), metals, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs) and dioxins (PCDD/Fs). Many of these have toxic properties including irritancy, immunotoxicity, mutagenicity, carcinogenicity and reproductive effects. The principal objective of this report is to provide authoritative information on the likely impacts on human health of pollutants released from modern MSW combustion plants.

This Institute for Environment and Health (IEH) report identifies ten pollutants emitted as a result of waste combustion, reviews the literature on their reported toxic effects and identifies the ways in which these pollutants might pose a risk to human health. Where indicated in the literature, this includes reference to sensitive population groups and to the health effects which may occur at low levels of exposure such as those which might result from MSW incineration.

The report takes account of the uncertainties and lack of consensus on some of these issues and, where appropriate, discusses the quality and quantity of data available. It highlights key issues and recommends priorities for further study.

IDENTIFYING KEY POLLUTANTS

The first part of the study involved collaboration with the Institute of Public and Environmental Health (IPEH) at the University of Birmingham (Harrad & Harrison, 1996). The following section gives a brief summary of the approach taken to identify key pollutants.

The IPEH team generated an initial core list containing all the pollutants identified as being produced by waste incineration, whether currently regulated by the Environment Agency or not. This list comprised over 60 pollutants or groups of pollutants and included emissions from the combustion of sewage sludge, chemical waste, clinical waste and municipal waste (Table 1.1).

Table 1.1 Initial list of pollutants from waste combustion

Pollutant class	Individual pollutants	
Particles and gases	CO, HCl, HF, NO_x (NO/NO_2), PM_{10}, SO_x (SO_2/SO_3), total particulates.	
Metals	Aluminium, antimony, arsenic, barium, beryllium, cadmium, chromium, cobalt, copper, iron, lead, manganese, mercury, nickel, selenium, strontium, thallium, tin, titanium, vanadium, zinc.	
Organic compounds	1,1,1-trichloroethane	chloromethane
	1,1,2,2-tetrachloroethane	chlorophenols
	1,1,2-trichloroethane	dichlorodifluoromethane
	1,1-dichloroethane	dichloromethane
	1,1-dichloroethene	diethyl phthalate ethylbenzenes
	1,2-dichloroethane	formaldehyde
	1,3-butadiene	hexachloroethane
	2,4-dinitrophenol	phenol
	acetonitrile	polybrominated dibenzodioxins/furans
	acrolein	polychlorinated biphenyls
	acrylonitrile	polychlorinated dibenzodioxins/furans
	benzene	polycyclic aromatic hydrocarbons
	bis(2-ethylhexyl)phthalate	tetrachloroethene
	bromomethane	toluene
	butan-2-one	trichloroethene
	carbon tetrachloride	vinyl chloride
	chlorobenzenes	xylenes
	chloroform	

Ground-level concentrations from a large incinerator were predicted for each pollutant and compared with the relevant ambient air quality standards or with appropriately modified occupational exposure limits. Those pollutants which demonstrated a high ratio of ground-level concentration to air quality standards were considered further. Dioxins, PCBs and PAHs were also included because of the high level of public concern surrounding them.

Disposal of liquid and solid residues from waste incineration, and subsequent exposure pathways, were also considered in the selection of key pollutants. At the end of this evaluation process 32 pollutants remained on the list for further consideration.

For each pollutant, data on incinerator emissions were combined with data on background levels in air, water, sediments, soil and plants to assess the likely changes in pollution levels as a result of unit waste combustion. Estimates of people's consumption of different foods and water and inhalation of air were then used to assess the relative significance of the various human exposure pathways.

RATIONALE FOR THE LIST OF TEN KEY POLLUTANTS

The ten pollutants considered to have the greatest potential impact on human health were then selected for detailed review. Two approaches were used to make the selection. The first considered the chemical profile of each substance, including its environmental persistence, bioaccumulation and the likelihood of its being produced by waste incineration in amounts sufficient to exceed short-term (1-hr average) or long-term (annual average) air quality standards* (Harrad & Harrison, 1996).

The second approach was based on the inherent toxicity of the individual pollutants. It focused on the International Agency for Research on Cancer (IARC) classification of chemicals with respect to carcinogenicity and the risk phrases contained in the Chemicals (Hazard Information and Packaging for Supply) Regulations (CHIP2, 1994).

Table 1.2 shows the ten pollutants and the rationale for their inclusion. There was no attempt to rank these ten pollutants in order of importance as the amounts emitted may vary between incinerators.

The substances in Table 1.2 are not the only ones that should feature in a formal risk assessment, because in certain cases other pollutants may be more important. Table 1.3 lists the remaining 22 pollutants not considered further in this report.

*Ambient exposure standards or guidelines were used where they exist. For chemicals without such standards, a combination of approaches was used to derive air quality standards (AQSs). Short-term AQSs were obtained by dividing HSE short-term exposure limits by a factor of ten to protect vulnerable groups of the general population. Long-term AQSs were derived by dividing occupational exposure standards by 100 for non-carcinogenic chemicals (two factors of ten to account for continuous exposure and sensitive groups, respectively) and by 500 for maximum exposure limits of carcinogenic chemicals.

Table 1.2 List of ten pollutants and rationale for their selection

Pollutant	Rationale
Cd	Possibly produced by waste incineration in amounts sufficient to exceed both LAQS and SAQS
Hg	Bioaccumulative; widespread opinion (especially in Scandinavia) that the existing body burden is too high
As	Carcinogenic; possibly produced by waste incineration in quantities sufficient to exceed LAQS
Cr	Carcinogenic; maximum GLC that could possibly arise from waste incineration is significantly higher than the LAQS
Ni	Carcinogenic; maximum GLC that could possibly arise from waste incineration is significantly higher than the LAQS
PCDD/Fs PAHs PCBs	Extreme public concern; also to varying degrees bioaccumulative, persistent and possibly produced in waste incineration in quantities sufficient to exceed LAQS
PM_{10} SO_2/SO_3	Possibly produced in waste incineration in amounts sufficient to exceed both LAQS and SAQS

From Harrad & Harrison (1996)

LAQS, long-term air quality standard; SAQS, short-term air quality standard; GLC, ground level concentration

Table 1.3 Subsidiary list of 22 pollutants not considered further

Be, Co, Cu, HCl, HF, Mn, NO_x (NO/NO_2), Pb, Sb, Se, Sn, Tl, V, Zn, acrolein[d], acrylonitrile, benzene[a], 1,3-butadiene[c], 1,2-dichloroethane[b], formaldehyde[b], 1,1,2,2-tetrachloroethane[d], vinyl chloride[a],

These substances were included for reasons other than their potential contribution to ambient air quality:

[a] IARC Group 1 carcinogen (carcinogenic to humans)

[b] IARC Group 2A carcinogen (probably carcinogenic to humans)

[c] IARC Group 2B carcinogen (possibly carcinogenic to humans and carries the CHIP2 risk phrase ‘may cause cancer’)

[d] Carries the CHIP2 risk phrase ‘very toxic by inhalation’

IDENTIFYING MAJOR ROUTES OF EXPOSURE

This section summarises the major exposure routes of the ten pollutants. A more detailed explanation is contained in Harrad & Harrison (1996). Where available, data on uptake by different routes are discussed in the sections covering individual pollutants.

Before it was possible to estimate the health effects of each pollutant it was important to identify the main exposure routes for both the general public and people living near waste incinerators. For PM_{10} and SO_2 , which are atmospheric pollutants, only the inhalation pathway was considered relevant. For the other pollutants the relative importance of the various exposure pathways was less obvious and was established from published data.

Three main forms of emission are relevant to assessing human exposure to the products of waste incineration:

- ❒ atmospheric releases from the stack in the form of particles and vapour;
- ❒ the disposal of ash and other residues from emission control devices; and
- ❒ waste water discharge.

Atmospheric emission is the most obvious exposure route. Exposure can occur by:

- ❒ direct inhalation;
- ❒ aerial deposition to water courses and subsequent consumption of contaminated water and fish;
- ❒ deposition to land used to grow food and subsequent consumption of the contaminated crops;
- ❒ deposition to pasture land, consumption of contaminated grass and soil by grazing animals and subsequent human consumption of contaminated meat and dairy produce; and
- ❒ deposition to soil and subsequent consumption of, or contact with, contaminated soil.

Exposure to pollutants from the disposal of arrested ash could potentially occur by:

- ❒ direct inhalation of fugitive emissions;
- ❒ deposition to land and consumption of contaminated plant, animal or dairy produce; and
- ❒ drinking contaminated groundwater.

Disposal of waste water to the sewerage system can expose people through the consumption of contaminated drinking water or the application of contaminated sewage sludge to land used to grow food crops.

Based on the available data, the two main routes of exposure to the ten pollutants considered here are inhalation and ingestion. Table 1.4 gives the approximate relative contributions of these two routes for the general population and for populations living around incinerators. Where data are given, it shows that for all pollutants except PM_{10} and SO_2 the major route of background and incremental exposure is ingestion, mostly of food.

For people living around incinerators, the total exposure consists of a background exposure and an incremental exposure. In the context of this report incremental exposure refers to the additional exposure, above that of the background, received by an individual living near a point source of the pollutant.

CADMIUM

Ingestion is the biggest source of background and incremental exposure to cadmium; drinking water and air inhalation are less important routes. Heavy smoking will contribute significantly to exposure and may be equal to or greater than exposure *via* drinking water.

Table 1.4 Relative contributions of inhalation and ingestion to background and incremental exposure for the ten pollutants

Pollutant	Population exposed	Relative exposure *via* ingestion (%)	Relative exposure *via* inhalation (%)
Cd	General population	Food > drinking water > air. Smoking is important	
	Population around incinerators	Similar to general population	Similar to general population
Hg	General population	Dental amalgams and diet are important. Exposure *via* inhalation is approximately four times greater than *via* drinking water	
	Population around incinerators	Similar to general population	Similar to general population
As	General population	Food > drinking water > air. Smoking is important	
	Population around incinerators	Similar to general population	Similar to general population
Cr	General population	Food > drinking water > air. Smoking is important	
	Population around incinerators	Similar to general population	Similar to general population
Ni	General population	Food > drinking water > air. Smoking is important	
	Population around incinerators	Similar to general population	Similar to general population
Dioxins/	General population	(98)	(2)
Furans	Population around incinerators	(94)*	(2)
PAHs	General population	(55, range 9.7–94)	(45, range 10–90)
	Population around incinerators	Similar to general population	Similar to general population
PCBs	General population	(97)	(3)
	Population around incinerators	(97)	(3)
PM_{10}	General population	(0)	(100)
	Population around incinerators	(0)	(100)
SO_2	General population	(0)	(100)
	Population around incinerators	(0)	(100)

Data from Harrad & Harrison (1996)

*Estimate for ingestion of plant and animal produce only. No estimate provided for ingestion of soil or water

MERCURY

Mercury occurs in three forms: elemental vapour and inorganic and organic compounds. Background exposure to total mercury occurs mainly through diet, with fish considered to be a significant source because of their ability to accumulate methylmercury formed from inorganic mercury by microbial activity in the aquatic environment. The WHO (1990) has suggested that the most important source of human exposure to mercury is dental amalgam, which produces elemental mercury vapour. In the absence of evidence to the contrary, the major routes of incremental exposure are assumed to be similar to those for background exposure.

ARSENIC

In descending order of importance, the major routes of background and incremental exposure to arsenic are considered to be food, drinking water and inhalation of outdoor air. Smoking is an important source of arsenic and, for heavy smokers, the exposure from smoking may exceed that received by inhaling outdoor air.

CHROMIUM

The significant exposure pathways for total chromium (Cr (VI) and Cr (III)) for background and incremental exposure are, in descending order, food, drinking water and inhalation. Smoking will also contribute to total chromium exposure. The toxicities of these two forms of chromium are very different (see Section 2.5) but little is known about the relative abundance of Cr (VI) and Cr (III) in the environment.

NICKEL

For nickel, ingestion of food, especially fruit and vegetables, is the most significant source of exposure for the general population. Exposures *via* drinking water and air inhalation are less important. Incremental exposure will also occur by the same routes. For heavy smokers, the additional exposure will be greater than background inhalation exposure and may exceed the level received *via* drinking water.

DIOXINS/FURANS AND PCBs

For dioxins/furans and PCBs the ingestion of food accounts for more than 95% of all exposure; meat and dairy products are significant sources. For people living or working near a point source of dioxins/furans the inhalation route may represent a greater proportion of the total incremental exposure than for the general population. However, ingestion remains the dominant route and probably accounts for 90% or more of the total exposure to these compounds, especially if the contamination of food produced near the source of the pollution is considered.

PAHs

Ingestion of food and inhalation represent the two main routes of exposure to PAHs for the general population. The ratio of ingestion to inhalation has been reported to range from 10%:90% to 90%:10%. Exposure *via* drinking water is considered to represent only a small fraction of total exposure.

For individuals living near a point source of PAHs, incremental exposure through both routes may be higher than for the general population. However, the relative contributions of the different exposure routes probably reflect those for the general population.

PM_{10} AND SO_2

Inhalation is the only relevant route of exposure to PM_{10} and SO_2, both for the general population and for individuals living near a point source. Some of the PM_{10} inhaled may subsequently be swallowed and could therefore be considered to be ingested, but this is likely to represent an extremely small and largely unquantifiable fraction of the total exposure via inhalation.

ASSESSING POTENTIAL HEALTH EFFECTS

As a first step in the review of the health effects of pollutants from waste incineration and the evaluation of the likely risk to human health, a literature search was undertaken which covered standard toxicological textbooks, biomedical bibliographical databases and both governmental and non-governmental official publications. Carcinogenic and non-carcinogenic endpoints

were included, as well as morbidity and mortality data, and where information was available the search took particular account of sensitive populations. The most recent high-quality reviews were identified and evaluated for comprehensiveness, quality and dose–response data. In some cases recently-published individual studies were included to complement the reviews.

Literature summaries were then prepared and presented to a group of invited experts at a technical workshop held in Leicester in January 1996. The aim of the workshop was to discuss, for each pollutant, data relating to dose–response relationships and exposure pathways for each identified health effect. Any uncertainties in the data and gaps in knowledge were identified and key areas for further research were recommended.

HOW THIS REPORT USES EPA/WHO CANCER RISK ESTIMATES

For the past two decades the US Environmental Protection Agency (EPA) has been using quantitative risk assessment for regulatory purposes. Over this period the EPA has standardised and formalised its approach, which until recently was based on a mathematical linearised multi-stage model (EPA, 1986). This approach tended to be very conservative. In the case of dioxins, for example, the WHO acceptable daily intake (ADI), based on a safety factor approach, is in the pg/kg/day range. The UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has endorsed the WHO figure. The ADI given by the EPA, however, was in the fg/kg/day range, which is lower by a factor of more than 1000 (see Section 2.7.4). Following a review by the National Research Council (NRC), however, the EPA has reappraised its methodology (EPA, 1996).

The WHO has calculated risk estimates based on carcinogenic effects for four of the ten pollutants considered in this report: arsenic, nickel, chromium and PAHs as benzo[*a*]pyrene. These have been determined on the basis of no threshold for effect (i.e. that there is no safe level) using an average relative risk model. The air quality guidelines are then presented in terms of incremental unit risks (usually expressed as the estimated number of excess cases of cancer when the population is exposed to a concentration of 1 $\mu g/m^3$ of the pollutant continuously for 70 years). No risk estimate was given for cadmium, as the data based on human studies were considered difficult to interpret (WHO, 1987).

Quantitative risk estimates may give an impression of accuracy that they do not warrant (WHO, 1987). Factors including inadequate exposure data and failure to account for the metabolic properties or modes of action of a chemical in the model used can produce errors and uncertainties. Quantitative risk estimates should therefore be used only as guidelines for comparing the relative risks of different pollutants, for establishing priorities or balancing risks with benefits, and no further interpretation should be placed on the figures.

A FORWARD LOOK

This report should help inform those responsible for making decisions on waste management, and other interested parties, about the health effects of pollutants released during incineration. It should also be useful in assessing the comparative benefits of alternative waste management strategies. The report may also aid the process of risk assessment, but only in conjunction with other information such as existing background levels of pollutants, actual exposure data and details of the exposed populations.

Although the primary concern of this study is pollutants released during MSW incineration, the initial list of pollutants included emissions from combustion of other wastes including sewage sludge, chemical and clinical waste. The conclusions of this report therefore apply in some measure to other waste combustion processes.

Because the UK has only recently introduced 'current practice' in pollution abatement for MSW incinerators, very few emissions data from these sources are available. Most of the published emissions data originated from incinerators with pollution abatement technology below current standards. These older incinerators are likely to have released significantly greater amounts of pollutants than current laws would allow: since the end of 1996 the Environment Agency has used Integrated Pollution Control to set more stringent limits for specific pollutants.

The ten pollutants identified in this study remain relevant to the consideration of potential health effects of emissions from modern MSW incinerators. In the future, however, tighter emission limits may have two effects. First, pollutants not considered here in detail will eventually constitute a greater proportion of total emissions and their health effects may therefore become relatively more important. Second, the new limits apply only to stack emissions, so the relative significance of the various exposure pathways may also change. Both these changes may affect future thinking on the relative importance of different pollutants.

REFERENCES

CHIP2 (1994) *Approved guide to classification and labelling of substances and preparations dangerous for supply*, Chemicals (Hazard Information and Packaging for Supply Regulations 1994), Health and Safety Commission, Sudbury, UK, HSE Books

EPA (1986) Guidelines for carcinogen risk assessment. *Federal Register, 51,* 33992–34003

EPA (1996) *Proposed guidelines for carcinogen risk assessment*, Washington DC, USA, Office of Research and Development, US Environmental Protection Agency

Harrad, S.J. & Harrison, R.M. (1996) *The health effects of the products of waste combustion*, available from the Institute of Public and Environmental Health, University of Birmingham

RCEP (1993) *Incineration of waste* (Royal Commission on Environmental Pollution, Seventeenth Report), London, UK, HMSO

WHO (1990) *Methylmercury* (International Programme on Chemical Safety, Environmental Health Criteria, 101), Geneva, Switzerland, World Health Organization

WHO (1997) *Air quality guidelines for Europe* (European Series No. 23), Copenhagen, Denmark, World Health Organization

2 Health effects of ten key pollutants from waste incineration

2.1 ESTIMATES OF BACKGROUND AND INCREMENTAL EXPOSURE

A qualitative assessment of the impact of pollutants from incinerators on the health of people living nearby requires a knowledge of the extra exposure, above background levels, caused by the incinerator.

The information used to assess this 'incremental' exposure comes from published studies. Unfortunately these data are incomplete, so the estimates cited below are very approximate. Published background estimates or measured levels of each of the ten pollutants considered in this report varied, in some cases, by several orders of magnitude. Estimates of incremental levels of exposure resulting from living near point sources of pollutants such as incinerators showed a similar variation.

Table 2.12.1 gives examples of background levels of the pollutants in air and estimates of average daily intakes. To indicate the relative contribution of incremental exposure to total exposure it is useful to consider both 'worst case' and average incremental levels, expressed as percentages relative to the background. It should be stressed that the worst-case scenario is calculated for a so-called maximally-exposed individual, considered to be a person living and working near a point source of pollution who is exposed solely by breathing the air coming from the source and by eating contaminated home-grown vegetables and meat, fish, milk and eggs from animals reared near the source.

For most of the key pollutants, where data are available, the worst-case estimates of incremental exposure *via* inhalation are less than 20% of background exposure. For PM_{10} and SO_2 the estimates rise to between 30% and 40% of background exposure levels. None of the estimates of likely average incremental exposures exceeds 5% of background levels for correctly-operated incinerators, and for

several of the metals considered here the true average incremental exposure may be only one-tenth of this or less. However, caution should be exercised since these incremental estimates are based mostly on exposure *via* inhalation, which may account for less than 10% of total exposure. The detailed modelling needed to assess the importance of other exposure routes has not been carried out.

Short reviews of the health effects of the ten key pollutants follow. In general, for each pollutant, there is a short introduction followed by sections on non-carcinogenic and carcinogenic effects, safety limits and guidelines*, a summary and a list of references. In some cases these sections are further subdivided.

* Exposure limits and guidelines referred to in this report include the occupational exposure standards (OES) and maximum exposure limits (MEL) set by the UK Health and Safety Executive (HSE). These limits may be set over a long term 8-hour time-weighted average (8-hr TWA) reference period or over a 15 minute reference period. Reference concentrations (RfC) and reference doses (RfD) are estimates of continuous exposures, *via* inhalation and ingestion respectively, that are likely to be without deleterious effects to the population, including sensitive subgroups.

Other agencies set different exposure guidelines and limits which are identified in the appropriate tables.

2.2 CADMIUM

2.2.1 INTRODUCTION

Cadmium is a metal that occurs naturally in the earth's crust, predominantly in the form of its chloride, oxide and sulphide. Industry uses cadmium on a large scale, mainly to produce alkaline batteries and industrial pigments but also in welding and electroplating (Savolainen, 1995). Cadmium can contaminate the environment through the application of phosphate fertilisers and sewage sludge to soils, and particularly through the burning of fossil fuels and the incineration of municipal waste (ATSDR, 1989). The cadmium species formed during combustion (principally the chloride and oxide) have important toxicological properties.

Because cadmium is so widely used and distributed, a large proportion of the population in industrialised countries is exposed to it. The general public comes into contact with cadmium primarily through food (cadmium is a constituent of normal foodstuffs, due to its uptake by plants), but cigarette smoking also exposes individuals to high levels of cadmium. A single cigarette can contain up to 2 µg of cadmium, up to 10% of which is absorbed. The estimated body burden of people who are not occupationally exposed to cadmium ranges from 5 mg to 40 mg. The body burden of smokers is approximately twice that of non-smokers (Lauwerys & Hoet, 1993).

The human body actually absorbs significantly less cadmium than the total daily intake through ingestion and inhalation; the rest is excreted naturally. For gastrointestinal exposure only approximately 5% of the cadmium eaten is absorbed, and for the respiratory route the figure is around 50% (see Table 2.2.1; WHO, 1992; Lauwerys & Hoet, 1993; Savolainen, 1995).

The highest cadmium intake from the diet is likely to occur in teenagers, because of their high caloric intake. The body burdens of iron and dietary zinc are also important in determining the extent of gastrointestinal absorption of cadmium.

For example, iron-deficient individuals can absorb as much as 24% of the cadmium in an oatmeal breakfast whereas iron-proficient individuals absorb less than 1%. The presence of gastrointestinal zinc can prevent the absorption of cadmium through the lumen wall (Jonnalagadda & Prasada Rao, 1993). Once absorbed, over 70% of cadmium is bound to red blood cells and transported to tissues. Cadmium stimulates the production of the peptide metallothionein, which sequesters cadmium within tissues (Lauwerys & Hoet, 1993).

The average mean annual concentration of cadmium in air at five UK sites in 1990 was determined to be approximately 0.005 µg/m^3 (see Table 2.12.1). Assuming that an individual breathes 20 m^3 of air per day and that 50% of the inhaled cadmium dose is absorbed (see Section 2.2.1), this equates to an intake of approximately 0.1 µg/person/day. The total upper bound intake from the diet has been estimated at 18 µg/person/day (see Table 2.12.1).

Table 2.2.1 Estimated exposure levels of different populations to cadmium

Exposed group	Estimated daily levels of cadmium absorbed (µg)		
	Inhalation	Ingestion	Total
General population (uncontaminated area)			
Non-smoking	0.04	0.6–1.3	0.64–1.34
Smoking	1–2	0.6–1.3	1.6–3.3
General population (contaminated area)			
Non-smoking	2	8–10	10–12
Smoking	3–4	8–10	11–14[a]
Occupational exposure			
Non-smoking	25–125	10–15	35–140
Smoking	[b]	10–15	–

From WHO (1992)

[a] Levels are unlikely to exceed 20 µg/day

[b] Tobacco carried by workers is likely to become contaminated and may contribute up to ten times more cadmium uptake than in normal conditions

2.2.2 NON-CARCINOGENIC EFFECTS

The non-cancer endpoints of cadmium toxicity have been well documented. Acute effects can be severe in people who are occupationally exposed or who have ingested cadmium accidentally. The development of chronic health effects is slow and may take decades. The dose levels at which these effects are manifest have been determined but it is difficult to ascertain whether significant health effects occur at non-occupational exposure levels.

ACUTE TOXICITY

In man, the acute effects of short-term high-level exposure to cadmium by inhalation and ingestion appear at the site of absorption, although renal and hepatic toxicities have been reported following ingestion (CEC, 1978).

CHRONIC TOXICITY

It is known that long-term exposure to cadmium results in renal and pulmonary toxicity. Of these two primary outcomes, respiratory ailments are more likely to affect the quality of an individual's life, although the kidney is the organ in which chronic toxicity is first seen (CEC, 1978).

Cadmium is not readily excreted from the body; its half-life in humans is at least ten years (Lauwerys & Hoet, 1993). Under conditions of chronic exposure cadmium continues to accumulate in the liver and kidneys throughout an individual's life (50% of the body burden is found in these two organs). Cadmium causes nephrotoxicity if its concentration in the kidney is above a threshold value. The primary lesion is renal dysfunction which results from irreversible damage to the tubular epithelium. This can give rise to secondary ailments such as kidney stones, and may cause debilitating skeletal effects believed to be due to cadmium's ability to disrupt the metabolism of vitamin D, which regulates the body's uptake of calcium. The estimated critical concentration above which renal toxicity is apparent as proteinuria is 200 mg cadmium/kg renal cortex. (WHO, 1992).

Respiratory effects are generally only associated with occupational exposure to cadmium aerosols and dust, although some studies have indicated that no threshold

exists for cadmium-induced pulmonary toxicity measured as airflow limitation, impaired gas transfer and increased lung volumes (Davison *et al.*, 1988). There is no evidence to suggest that pulmonary toxicity occurs after ingestion.

HEALTH EFFECTS FOLLOWING OCCUPATIONAL EXPOSURE

Emphysema is known to occur in individuals exposed to high levels of cadmium (Davison *et al.*, 1988). CEC (1978) estimated that repeated eight-hour exposures to concentrations above 20 µg/m^3 over a period of less than 20 years could induce a slight functional change in the lungs of susceptible individuals; the ATSDR (1989), however, reported that this level poses little risk of renal and pulmonary injury. Other studies have indicated that subclinical effects occur at cumulative doses of 100–300 µg/m^3.yr, corresponding to exposure limits of 2.2 µg/m^3 and 6.6 µg/m^3 respectively for an exposure over eight hours per day for 45 years (Savolainen, 1995).

Mason and co-workers calculated a cumulative exposure index of 1100 µg/m^3.yr when analysing total urine protein and the tubular reabsorption of proteins in male copper-cadmium alloy workers (Mason *et al.*, 1988). Similar values have been calculated by other groups (Falck *et al.*, 1983; Elinder *et al.*, 1985a).

A recent study of a group of male workers employed at a cadmium smelter noted that urinary levels of ß-N-acetylglucosamidase (NAG-B) rose in association with urinary cadmium levels, and that this occurred at exposure levels encountered by the general public. There seemed to be no threshold for this effect. The authors postulated that at low urinary cadmium levels (around 4 µg/g creatinine) apoptotic mechanisms were responsible for the presence of cadmium and NAG-B in urine (Bernard *et al.*, 1995).

HEALTH EFFECTS FOLLOWING ENVIRONMENTAL EXPOSURE

Diet is the main source of cadmium exposure for the general public. At this level of exposure, renal toxicity is the endpoint of concern in assessing the impact of cadmium on the general population. Using a worst-case estimate of particulate emissions it has been calculated that the maximum flue gas concentration of cadmium emitted from an incinerator may be as high as 11 mg/m^3 (Harrad & Harrison, 1996). Although it is not clear what level of exposure might result from

this level of cadmium in the flue gas, some occupational studies suggest that no threshold exists for pulmonary toxicity to cadmium fume and dust, so respiratory effects cannot be discounted.

Cadmium is known to accumulate markedly in the soil around zinc smelters (WHO, 1992). Staessen and colleagues investigated the effects of cadmium in a highly-exposed population surrounding three zinc smelters and compared them with control populations more than 10 km from the plants (Staessen *et al.*, 1994). The two groups showed a small but statistically significant difference in their levels of urinary proteins and enzymes. The implications of these findings for long-term health effects are not clear.

2.2.3 CARCINOGENIC EFFECTS

Cadmium has been demonstrated to be genotoxic, but not mutagenic, in *in vitro* assays. There are conflicting epidemiological data on the link between cadmium exposure and cancer in people who have been exposed either occupationally or accidentally. Whilst some studies have shown that the risk of lung cancer increases in workers occupationally exposed to cadmium aerosols and dust by inhalation (Fan, 1990), cadmium has not been shown to be carcinogenic when ingested. The inability to rule out confounders such as arsenic exposure and smoking (which act synergistically with cadmium in inducing lung cancer) has limited the interpretation of studies showing an association between lung cancer and cadmium exposure.

The ATSDR estimates that the upper-bound lifetime risk for lung cancer is 1 in 10^6 at a concentration of approximately 1 ng/m^3 in air (ATSDR, 1991), and that lifelong inhalation of 1 µg/m^3 cadmium increases the risk by 2 in 1000 (ASTDR, 1989). These upper-bound risk estimates can be compared with the WHO assumptions that the air concentration of cadmium is 10 ng/m^3 in uncontaminated areas, 0.5 µg/m^3 in contaminated areas and 10–50 µg/m^3 in some workplaces (WHO, 1992). In view of the conservatism inherent in these estimates it is difficult to assess their value, but near point sources of cadmium the risk of lung cancer could increase significantly.

Some studies have implicated cadmium in prostate cancer, but the link is not clear and many other factors are thought to be important in the aetiology of this disease. Elinder (1985b) combined cohort data from pre-1985 studies and

concluded that there was an association between cadmium exposure and prostate cancer, though other authors have questioned the validity of combining these studies (Waalkes & Rehm, 1994). Other studies linking cadmium exposure to prostate cancer (WHO, 1992) have also been refuted by Waalkes & Rehm (1994).

WHO (1992) has summarised available epidemiological data on occupational exposure to cadmium; the levels of exposure range from 60–4000 $\mu g/m^3$. In summary this report states that occupational studies show the existence of a link between lung cancer and exposure to cadmium, with a possible dose–response relationship; the latter has not, however, been corroborated by other studies.

The EPA quotes an inhalation unit risk of developing cancer of 1.8×10^{-3} per $\mu g/m^3$, based on human data (IRIS, 1996). A more conservative inhalation unit risk of 9.2×10^{-2} per $\mu g/m^3$ was obtained from animal studies conducted by Takenaka *et al.* (1983). The EPA felt that the available human data were more reliable because of the variations in response and type of exposure between different cadmium species (cadmium salts, cadmium fume and cadmium oxide).

The EPA has estimated an air concentration of 0.6 ng/m^3 to be associated with a risk level of 1 in 10^6 (IRIS, 1996). This was based on a study of white male workers conducted by Thun *et al.* (1985) in which lung, bronchial and tracheal cancer mortality was documented after inhalation of cadmium fumes.

On the basis of the evidence linking cadmium to lung cancer, IARC (1993) classified cadmium as a Group 1 (human) carcinogen. The EPA has classified cadmium as a probable human carcinogen (class B1) on the basis that although there are uncertainties in the limited human data there is strong evidence that cadmium is an animal carcinogen (IRIS, 1996).

2.2.4 EXPOSURE LIMITS AND GUIDELINES

Better industrial hygiene has meant that current occupational exposure levels for cadmium have fallen to 20–50 $\mu g/m^3$. This is still high enough to cause proteinuria to develop over a period of 10–20 years' exposure (WHO, 1992).

The National Institute of Occupational Safety and Health recommends that because of the carcinogenic potential of cadmium, controls should be used to reduce worker exposure to the fullest extent possible.

Table 2.2.2 shows the exposure guidelines set by the various limits and UK and US government agencies.

Table 2.2.2 Exposure limits and guidelines for cadmium

Agency	Form of cadmium	Exposure limit/guideline	Reference
HSE	Cadmium and cadmium compounds (except oxide fume, sulphide and sulphide pigments)	25 µg/m^3 (MEL; 8-hr TWA RP)	HSE, 1996
	Cadmium oxide fume	25 µg/m^3 (OES; 8-hr TWA RP)	"
		50 µg/m^3 (OES; 15-min RP)	"
	Cadmium sulphide and sulphide pigments	40 µg/m^3 (OES; 8-hr TWA RP)	"
EPA	Cadmium in drinking water	5 µg/l	ATSDR, 1993
		0.5 µg/kg bw/day (RfD)[a]	IRIS, 1996
	Cadmium in food	1 µg/kg bw/day (RfD)[a]	"
OSHA[b]	Cadmium dust	200 µg/m^3	ATSDR, 1993
	Cadmium fumes	100 µg/m^3	

[a] Based on NOAEL in both animals and humans, and assuming a 2.5% Cd absorption from food, compared with 5% from water
[b] Occupational Safety and Health Administration

RP, reference period

2.2.5 SUMMARY

The non-carcinogenic effects of cadmium that have been shown to occur at occupational levels are respiratory illness (emphysema) and kidney dysfunction. The renal effects have been shown to have a threshold that is above current UK occupational exposure limits. A threshold has not been demonstrated for the less severe respiratory effects seen at lower occupational exposure levels and therefore it is possible that such effects could occur at environmental exposure levels.

Occupational exposure has also been associated with increased lung cancer risk. Evidence of proteinuria has been found in some individuals in highly exposed populations surrounding zinc smelters, but the implications of these effects for people living around incinerators and the general population is not clear.

2.2.6 REFERENCES

ATSDR (1989) *Public health statement for cadmium*, Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services

ATSDR (1991) *Draft toxicological profile for cadmium*, Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services

ATSDR (1993) *ToxFAQs fact sheet on cadmium*, Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services

Benard, A., Thielemans, N., Roels, H. & Lauwerys, R. (1995) Association between NAG-B and cadmium in urine with no evidence of a threshold. *Occup. Environ. Med.*, *52*, 177–180

CEC (1978) *Criteria (dose/effect relationships) for Cadmium*, Oxford, UK, Pergamon Press

Davison, A.G., Newman Taylor, A.J., Darbyshire, J., Chettle, D.R., Guthrie, C.J.G., O'Mally, D., Mason, H.J., Fayers, P.M., Venables, K.M., Pickering, C.A.C., Franklin, D., Scott, M.C., Holden, H., Wright, A.L. & Gompertz, D. (1988) Cadmium fume inhalation and emphysema. *Lancet*, *1*, 663–667

Elinder, C.-G., Edling, C., Lindberg, E., Kagedal, B. & Vesterberg, O. (1985a) $ß_2$ Microglobulin among workers previously exposed to cadmium: follow up and dose–response analysis, *Am. J. Ind. Med.*, *8*, 553–564

Elinder, C.,-G., Kjellstrom, T., Hogstedt, C., Andersson, K. & Sprang, G. (1985b) Cancer mortality of cadmium workers. *Brit. J. Ind. Med.*, *42*, 651–655

Falck, F.Y., Fine, L.J., Smith, R.G., McClatchey, K.D., Annersley, T., England, B. & Schonk, A.M. (1983) Occupational cadmium exposure and renal status. *Am. J. Ind. Med.*, *4*, 541–549

Fan, A.M. (1990) The carcinogenic potential of cadmium, arsenic and selenium and the associated public health and regulatory implications. *J. Toxicol. Sci.*, 15 162–175

Harrad, S.J. & Harrison, R.M. (1996) *The health effects of the products of waste combustion*, available from the Institute of Public and Environmental Health, University of Birmingham, UK

HSE (1996) *Occupational exposure limits* (Health and Safety Executive EH40/96), Sudbury, UK, HSE Books

IARC (1993) *IARC monographs on the evaluation of carcinogenic risks to humans*, Vol 58, *Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry*, *cadmium and cadmium compounds*, Lyon, France, International Agency for Research on Cancer, pp 119–237

IRIS (1996) *Integrated risk assessment system, cadmium*, US Environmental Protection Agency, online search conducted January 1996

Jonnalagadda S.B. & Prasada Rao P.V.V. (1993) Toxicity, bioavailability and metal speciation. *Comp. Biochem. Physiol.*, *106C*, 585–595

Lauwerys, R.R. & Hoet, P. (1993) *Industrial Chemical Exposure: Guidelines for Biological Monitoring*, (Second Edition), London, UK, Lewis Publishers

Mason, H.J., Davison, A.G., Wright, A.L., Guthrie, C.J.G., Fayers, P.M., Venables, K.M., Smith, N.J., Chettle, D.R., Franklin, D.M., Scott, M.C., Holden, H., Gompertz, D. & Newman-Taylor, A.T. (1988) Relations between liver cadmium, cumulative exposure, and renal function in cadmium alloy workers. *Brit. J. Ind. Med.*, *45*, 793–802

Savolainen, H. (1995) Cadmium-associated renal disease. *Renal Failure*, *17*, 483–487

Staessen, J.A., Lauwerys, R.R., Ide, G., Roels, H.A. Vyncke, G. & Amery, A. (1994) Renal function and historical environmental cadmium pollution from zinc smelters. *Lancet*, *343*, 1523–1527.

Takenaka, S., Oldiges, H., Konig, H., Hochrainer, D. & Oberdorster, G. (1983) Carcinogenicity of cadmium aerosols in Wistar rats. *J. Natl. Cancer Inst.*, *70*, 367–371

Thun, M.J., Schnorr T.M., Smith, A.B. & Halperin, W.E. (1985) Mortality among a cohort of US cadmium production workers: an update. *J. Natl. Cancer Inst.*, *74*, 325–333

Waalkes, M.P. & Rehm, S. (1994) Cadmium and prostate cancer. *J. Toxicol. Environ. Health*, *43*, 251–269

WHO (1992) *Cadmium* (International Programme on Chemical Safety, Environmental Health Criteria, 134*)*, Geneva, Switzerland, World Health Organization

2.3 MERCURY

2.3.1 INTRODUCTION

Mercury is a metal present in the environment from both natural and anthropogenic sources. It is liquid at standard temperature and pressure. It arises naturally from volcanic gases as a result of the degassing of the earth's crust and also from evaporation from the oceans (WHO, 1991). Human exposure can be to metallic mercury, mercury vapour, inorganic salts or organic mercury compounds.

Exposure to mercury vapour has occurred in many settings and its toxicity is well described. Approximately 80% of the mercury vapour inhaled is absorbed through the lungs. It is known that non-ionic mercury vapour can cross the placental barrier, thus exposing the fetus. Uptake of mercury vapour *via* the skin is minimal (about 1% of the uptake by inhalation). Absorption of liquid metallic mercury from the gastrointestinal tract is poor, thus limiting its toxic effects.

Inorganic mercury salts are more toxic than metallic mercury on ingestion because of their greater solubility (Little, 1995); estimates of absorption efficiency in the gastrointestinal tract vary from 7% to 10% (WHO, 1991). Aerosols of inorganic mercury salts are also absorbed by the lungs; the rate at which this occurs depends on particle size.

Organomercurials, unlike inorganic mercury compounds, are almost completely absorbed in the gastrointestinal tract and easily cross the blood-brain barrier (Carpenter, 1994). Inorganic mercury is converted by microbial activity to methylmercury in aquatic ecosystems, and this is known to bioaccumulate in fish.

The effects of eating fish contaminated with methylmercury have been reported, mainly after severe pollution episodes. Most of the available data on the effects on humans of exposure to mercury come from occupational exposure (e.g. chloralkali plant workers, dentists, instrument manufacturers and lamp manufacturers; WHO,

1991). In this review the primary focus is on low-level occupational exposure and dental amalgam, an important source of low-level exposure for the general population. Incidents of methylmercury poisoning are also briefly considered.

The average mean annual concentration of mercury in air at nine UK sites between 1970 and 1989 was approximately 0.00025 µg/m^3 (see Table 2.12.1). Assuming that 20 m^3 of air is breathed by an individual per day and that 80% of the inhaled mercury dose is absorbed, this equates to an intake of approximately 0.005 µg/person/day. The total upper bound intake from the diet has been estimated as 2 µg/person/day (see Table 2.12.1). In people who are not occupationally exposed to mercury the concentration of mercury in urine is usually less than 5 µg/g creatinine (Lauwerys & Hoet, 1993).

2.3.2 NON-CARCINOGENIC EFFECTS

ACUTE TOXICITY

Severe toxicity, including interstitial pneumonitis and more general impairment of pulmonary function, has been recorded in workers exposed to levels of elemental mercury in the range 1.1–44 mg/m^3 (WHO, 1991). In doses of one or more grammes inorganic mercury compounds cause necrosis of the gastrointestinal mucous membrane and sometimes lethal damage to the renal tubules. In a study of 18 cases of human poisoning following ingestion of mercuric chloride, the lethal doses ranged from 29–50 mg/kg body weight; the most common autopsy findings were gastrointestinal and renal lesions (WHO, 1991).

CHRONIC TOXICITY AND OTHER EFFECTS

The nervous system is generally considered to be the target organ for chronic mercury toxicity. Symptoms of exposure include irritability, excitability and shyness (erethism); continued low-level exposure produces a fine tremor which spreads from the hands to the eyelids and tongue, and in more severe cases violent muscular spasms occur. Other important toxicological effects of mercury exposure are renal effects, including tubular damage and auto-immune glomerular nephritis, contact dermatitis and acrodynia (a disease of infancy, characterised by pain and

swelling in fingers and toes). Miscarriages and developmental abnormalities have been reported in some studies of occupationally-exposed groups, although these effects were not found in other investigations. In the case of methylmercury, the nervous system is also the main site of toxic effects; effects on neural development arising from fetal exposure are of special concern (WHO, 1990). Data from both occupational and environmental exposure are summarised below.

HEALTH EFFECTS FOLLOWING OCCUPATIONAL EXPOSURE

Many of the studies on occupational exposure to mercury are concerned with chloralkali and dentistry workers. Chloralkali workers are usually exposed to levels of mercury below 50 μg/m^3, although levels may exceed 100 μg/m^3 where industrial hygiene is poor (WHO, 1991). The current UK Occupational Exposure Standard is 25 μg/m^3 (8-hr TWA reference period). Table 2.3.1. shows selected data on occupational exposure levels and health effects.

WHO (1991) broadly categorised exposure-effect relationships for inorganic mercury. The WHO report stated that when exposure to mercury vapour is above 80 μg/m^3 (corresponding to a urine mercury level of 100 μg/g creatinine) there is a high probability of developing the classical signs of mercury vapour poisoning, such as tremor, erethism and proteinuria. Exposure in the range of 25–80 μg/m^3, which corresponds to a level of 30–100 μg mercury/g creatinine, is considered to increase the incidence of certain less toxic effects that do not lead to overt clinical impairment (subtle defects in psychomotor performance, objectively detectable tremor and evidence of impaired nerve conduction velocity) in particularly sensitive individuals. Effects of mercury vapour exposure at levels which correspond to urinary mercury levels of less than 30–50 μg/g creatinine have not been identified; there is a notable lack of appropriate epidemiological data (WHO, 1991).

Some studies have found an association between the occurrence of miscarriages and occupational exposure to mercury vapour, particularly in dentists and dental nurses, although others have not. On this issue the WHO is prudent and recommends that pregnant women should be exposed as little as possible to mercury vapour (WHO, 1991).

A particular problem in the risk assessment of inorganic mercury is that it can give rise to immunotoxic and allergic effects which are partly genetically related. It is possible that a small fraction of the population may be particularly sensitive, as has been observed in animal studies. Based on an evaluation in animals, the most

Table 2.3.1 Representative studies on inorganic mercury exposure and health effects where some estimate of environmental levels is presented

Nature of exposure	Study type and sample size	Exposure estimate	Effect	Comments
Cottage mercury smelting industry	Case histories	Up to 600 µg/m^3 mercury vapour	'Classical symptoms' of mercury poisoning	
Chloralkali factory workers, USA	Epidemiological *n* = 567	Mercury vapour no range given	0.1 mg/m^3 was found to be the threshold for significant effects (not inclusive of subjective symptoms)	Dose–response demonstrated
Chloralkali, fluorescent tube and acetaldehyde production plant workers	Epidemiological *n* = 26 with a control group	Mercury vapour 26 µg/m^3 based on personal monitoring	Increased incidence of hand tremor	
Chloralkali industry workers	Epidemiological *n* = 81	Mercury vapour concentrations ranged from 0.06–0.3 mg/m^3	15 cases of glomerular proteinuria among 81 examined. Increased levels of certain lysosomal enzymes were also found in plasma	No control group mentioned

Data from WHO (1991)

sensitive adverse effect is mercury-induced auto-immune glomerulonephritis; the first stage in this pathological process is the production of IgG antibodies and their deposition at the glomerular basement membrane (WHO, 1991).

The effects of low-level mercury exposure on behaviour have been recently investigated among dentists and workers in a fluorescent lamp factory. Echeverria *et al.* (1995) conducted a stratified cross-sectional study as part of the American Dental Association's (ADA) Health Screening. Behaviour assessments of 19 exposed dentists (mean urinary mercury = 36 µg/l) were compared with those of 20 unexposed dentists, who had no detectable levels of mercury in their urine. After controlling for the effects of age, race, gender and alcohol consumption, urinary mercury dose-effects were reported for poor mental concentration, emotional lability, somatosensory irritation and mood scores. Individual tests for cognition and motor changes were not significantly associated with urinary mercury, although there were significant associations with scores for combinations of tests.

Liang *et al.* (1993) used a computer-administered neurobehavioural evaluation system to assess the psychological effects of low-level mercury exposure in a group of workers (n = 88, 19 men and 69 women) exposed to mercury vapour (mean duration of exposure was 10.4 years and mean level of mercury vapour was 33 µg/m^3). In terms of mood states, the scores for fatigue and confusion were significantly higher than controls; neurobehavioural performance, after taking chronological age into account, was also significantly impaired in those exposed. These two studies are both at occupational exposure levels and the significance of the test results in relation to the general population is unclear.

Renal damage and behavioural effects are the key health effects of concern for low-level occupational exposure. Using animal lowest observed adverse effect level (LOAEL) data, human equivalent LOAELs have been determined for kidney effects. The oral exposure equivalent for humans was determined to be 15.8 mg/day; the 24-hour general population inhalation exposure and the 8-hour work-day inhalation exposure equivalents were calculated to be 69 µg/m^3 and 139 µg/m^3 respectively (WHO, 1991). More recently, urinary thresholds for nephrotoxicity and behavioural effects have been reported to be 50 µg/g creatinine (Price *et al.*, 1996) and 36 µg/l (Echeverria *et al.*, 1995) respectively. According to data reviewed in Lauwerys & Hoet (1993), these urinary levels equate to exposure levels in environmental air of approximately 41 µg/m^3 and 22.5–36 µg/m^3 respectively.

HEALTH EFFECTS FOLLOWING ENVIRONMENTAL EXPOSURE

The most important sources of environmental human exposure to mercury are probably dental amalgam and methylmercury in fish products.

Dental amalgam

The possible health impacts of dental amalgam have been reviewed recently by several authors (WHO, 1991; Eley & Cox, 1993; Eneström & Hultman, 1995). Eley & Cox (1993) listed kidney dysfunction, neurotoxicity, reduced immunocompetence, increased stillbirths, birth defects and general health as the most important possible health concerns associated with dental amalgam. They concluded that if dental amalgam does cause problems, only a small, susceptible proportion of the population is likely to be affected.

Eneström & Hultman (1995) specifically reviewed effects on the immune system. They concluded that there was sufficient evidence that rare instances of type I hypersensitivity (immediate, anaphylactic reactions) to mercury do occur, as well as infrequent cases of oral and systemic type IV hypersensitivity. The situation is less clear for auto-immune and type III (immune complex mediated) reactions, and for the possible influence of dental amalgam components on markers for T and B cell immune function.

Studies in rodents have demonstrated that genetic factors, particularly MHC genes, affect the outcome of mercury accumulation in the body with respect to adverse impacts on the immune system. If a safety factor of ten is applied for transforming data from animals to humans, and another factor of ten is applied to convert an LOAEL to a no observed adverse effect level (NOAEL), the allowable daily intake of mercury from deliberate mercury exposure would be 11–17 µg/day for an ordinary adult.

Methylmercury

Methylmercury is formed by the microbial conversion of inorganic mercury, chiefly in aquatic sediments but also in the water column. Methylmercury bioaccumulates in fish. The nervous system is the principal target tissue for the effects of methylmercury in humans. Early effects are non-specific symptoms such

as paresthesia (abnormal sensations such as burning and prickling), malaise and blurred vision. Subsequently, signs appear including concentric constriction of the visual field, deafness, dysarthria (speech defect due to nervous system damage) and ataxia (failure of muscular coordination). In the worst cases the patient may go into a coma and ultimately die. The developing nervous systems of children are known to be more sensitive to mercury than the adult nervous system; severe neurological defects have been recorded among children born to mothers who exhibited only mild signs of mercury poisoning (WHO, 1990).

There have been two serious incidents where human populations have been exposed to methylmercury with severe consequences. The first of these occurred in the 1950s when people in Minamata, Japan, were poisoned after eating fish and shellfish contaminated with methylmercury. The second was in Iraq in 1971–1972 when imported methylmercury-coated seeds for planting were consumed by mistake, resulting in at least 400 deaths.

2.3.3 CARCINOGENIC EFFECTS

Methylmercury has been classified by IARC as possibly carcinogenic to humans (Group 2B). Metallic mercury and inorganic mercury compounds were not classifiable as to their carcinogenicity to humans (Group 3; IARC, 1993). The EPA has not classified mercury in terms of its human carcinogenicity owing to a lack of human and animal data (IRIS, 1996).

Boffetta *et al.* (1993) concluded that data on the carcinogenicity of mercury was sparse, but that the few available studies strongly suggest that mercury compounds are genetically active in humans and other species. They concluded that studies on mice indicate carcinogenic activity for methylmercury in the kidneys. However, data for other species and sites are inconclusive. Human epidemiological studies are not conclusive, however, as some have focused on occupational groups (chloralkali workers, dentists and dental nurses, and nuclear weapons workers) which have relatively low levels of mercury exposure; these are of limited value for the evaluation of carcinogenicity.

2.3.4 EXPOSURE LIMITS AND GUIDELINES

The WHO (1987) concluded that because there was a lack of quantitative information on the consequences of the deposition of mercury from outdoor air, no ambient air guideline could be proposed. The WHO did set a guideline for the protection of human health from the effects of mercury in indoor air; this was 1 µg mercury per m^3 as an annual average, irrespective of the chemical form of the mercury in the air. Table 2.3.2 shows exposure limits and guidelines set by the UK and US government agencies and the WHO.

Table 2.3.2 Exposure limits and guidelines for mercury

Agency	Form of mercury	Exposure limit/guideline	Reference
HSE	Mercury and mercury compounds except alkyls	0.025 mg/m^3 (OES; 8-hr TWA RP)	HSE, 1996
	Mercury alkyls	0.01 mg/m^3 (OES; 8-hr TWA RP) 0.03 mg/m^3 (OES; 15-min RP)	"
OSHA	Mercury vapour	0.05mg/m^3	IRIS, 1996
NIOSH	Mercury vapour	0.05 mg/m^3	IRIS, 1996
WHO	Mercury in indoor air	1 µg/m^3	WHO, 1987

2.3.5 SUMMARY

Renal damage and subtle behavioural effects are the key health effects of concern at low levels of exposure to mercury. In recent studies, urinary thresholds of mercury for nephrotoxicity and behavioural effects have been reported to be 50 µg Hg/g creatinine and 36 µg/l urine respectively, although the significance of these effects with respect to the general population (whose urinary mercury concentration is usually less than 5 µg/g creatinine) is unclear.

2.3.6 REFERENCES

Boffetta, M.D., Merler, E. & Vainio, H. (1993) Carcinogenicity of mercury and mercury compounds. *Scand. J. Work. Environ. Health*, *19*, 1–7

Carpenter, D.O. (1994) The public health significance of metal neurotoxicity. *Cell. Mol. Neurobiol.*, *14*, 591–597

Echeverria, D., Heyer, N.J., Martin, M.D., Naleway, C.A., Woods, J.S. & Bittner, A.C. (1995) Behavioural effects of low-level exposure to Hg^o among dentists. *Neurotoxicol. Teratol.*, *17*, 161–168

Eley B.M. & Cox S.W. (1993) The release, absorption and possible health effects of mercury from dental amalgam: a review of recent findings (erratum to the original review published on September 11, 1993). *Brit. Dental J.*, *175*, 355–362

Eneström, S. & Hultman, P. (1995) Does amalgam affect the immune system? A controversial issue. *Int. Arch. Allergy. Immunol.*, *106*, 180–203

HSE (1996) *Occupational exposure limits 1996* (Health and Safety Executive EH40/96), Sudbury, UK, HSE Books

IARC (1993) *IARC monographs on the evaluation of carcinogenic risk to humans*, Vol 58, *Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry*, Lyon, France, International Agency for Research on Cancer

IRIS (1996) *Integrated risk assessment system, mercury*, US Environmental Protection Agency, Online search conducted January 1996

Lauwerys, R.R. & Hoet, P. (1993) *Industrial Chemical Exposure: Guidelines for Biological Monitoring* (Second Edition), London, UK, Lewis Publishers

Liang, Y., Sun, R., Sun, Y., Chen, Z. & Li, L. (1993) Psychological effects of low level exposure to mercury vapour: application of a computer-administered neurobehavioral evaluation system. *Environ. Res.*, *60*, 320–327

Little, D.N. (1995) Children and environmental toxins. *Primary Care*, *22*, 69–79

Price, R.G., Taylor, S.A., Chivers, I., Arce-Tomas, M., Franchini, I., Alinovi, R., Carrazzini, S., Bergamaschi, E., Mutti, A., Vettori, M.V., Lauwerys, R., Bernard, A., Roels, H., Thielmans, N., Hotz, Ph., De Broe, M.E., Elseviers, M.M., Nuyts, G.D., Gelpi, E., Hotter, G., Rosello, J., Ramis, I., Stolte, H., Fels, L.M. & Eisenberger, U. (1996) Development and validation of new screening tests for nephrotoxic effects. *Human Exp. Toxicol.*, *15*, (suppl 1), S10–S19

WHO (1987) *Air quality guidelines for Europe* (European Series No. 23), Copenhagen, Denmark, World Health Organization Regional Office for Europe

WHO (1990) *Methylmercury* (International Programme on Chemical Safety, Environmental Health Criteria, 101), Geneva, Switzerland, World Health Organization

WHO (1991) *Inorganic mercury* (International Programme on Chemical Safety, Environmental Health Criteria, 101), Geneva, Switzerland, World Health Organization

2.4 ARSENIC

2.4.1 INTRODUCTION

Many forms of arsenic are known, both inorganic and organic, and the human metabolism and absorption of these varies. Arsenic is ubiquitous in the environment. Inorganic arsenic is found chiefly as metallic arsenides, which usually occur in isomorphous mixtures with sulphides (WHO, 1992). In soils and aquatic environments, microbial activity converts inorganic arsenic to organic species which tend to bioaccumulate in aquatic organisms. Probably the most important industrial product is arsenic (III) oxide.

In man, inhaled, soluble forms such as oxides and arsenites are absorbed rapidly from the lungs, whereas less soluble forms may be retained for much longer. Over 90% of an ingested dose of dissolved trivalent or pentavalent arsenic is absorbed from the digestive tract. Organic arsenic is generally absorbed well in the digestive tract, although this depends on the specific form. Few data are available on the uptake of arsenic compounds *via* the skin (WHO, 1981; 1992).

Most published information on the effects of chronic arsenic exposure is concerned with copper smelter workers, vine growers, users of arsenic-containing medicines (Fowler's solution) and people who have drunk contaminated well-water.

The average mean concentration of arsenic in air at ten UK sites measured over the period 1970–1989 was approximately 0.016 µg/m^3 (see Table 2.12.1). Assuming that 20 m^3 of air is breathed by an individual per day and that 100% (worst-case estimate) of the inhaled arsenic dose is absorbed, this equates to an intake of approximately 0.32 µg/person/day. The total upper bound intake from the diet has been estimated as up to 70 µg/person/day (see Table 2.12.1).

2.4.2 NON-CARCINOGENIC EFFECTS

ACUTE TOXICITY

One of the main acute effects of inorganic arsenic ingestion is gastrointestinal damage, resulting in severe vomiting and diarrhoea. Other acute symptoms include muscular cramps, facial oedema, and cardiac abnormalities. When arsenic is taken orally, its toxic effects are largely determined by the solubility of the particular chemical form. The acute fatal dose of ingested arsenic (III) oxide for man has been reported to range from 1–2.5 mg/kg body weight (WHO, 1981). A National Research Council of Canada review on arsenic gave 5–50 mg as an acute lethal dose (NRCC, 1978). In an incident in Japan, 417 patients were poisoned by contaminated soy sauce. The average estimated intake was 3 mg of arsenic per person (valence state unknown) daily, for 2–3 weeks. The main health effects included facial oedema, anorexia, upper respiratory symptoms, skin lesions, inflammation of the nerves and abnormal electrocardiograms (WHO, 1981).

CHRONIC TOXICITY

The chronic health effects of exposure to inorganic arsenic involve mainly the respiratory, skin, vascular and haematopoetic systems (WHO, 1981).

Irritant arsenic compounds such as arsenic (III) oxide can cause local damage to the respiratory system. Changes in the nasal mucosa and signs of tracheobronchitis and pulmonary insufficiency have been recorded in copper smelter workers who worked in an environment where arsenic levels generally did not exceed 0.5 mg/m^3 (WHO, 1981)

The main effect on the skin of chronic arsenic exposure is hyperkeratosis of the palms of the hands and soles of the feet. A dose–response relationship was found between the amount of arsenic ingested and the incidence of palmoplantar hyperkeratosis in 262 patients treated 6–26 years earlier for chronic dermatoses with diluted Fowler's solution (3.8 g As/l). In one patient a cumulative intake of about 0.46 g of arsenic over 2.5 years resulted in keratosis. Hyperkeratosis has also been recorded in German vine growers who ingested an estimated total of 5.7–133 g of arsenic in insecticide-contaminated beverages (see page 50). Symptoms appeared 3–31 years from the beginning of the exposure.

There have also been several recorded incidents of liver damage caused by trivalent inorganic arsenic; a common sign is portal hypertension without signs of liver cirrhosis. In a study on copper smelter workers, those with the highest urinary levels of arsenic (mean 82.6 µg/l) had elevated levels of the liver enzymes glutamate transaminase and lactate dehydrogenase in serum; the level of exposure to arsenic was moderate in all cases (<13 µg/m^3 as a 6-hr average).

A high prevalence of a peripheral vascular disease called 'black-foot disease' was found in a population living in Taiwan, where the arsenic levels in well-water used for drinking ranged from 0.01–1.82 mg/l but were mainly between 0.4–0.6 mg/l. An approximately linear increase in the prevalence of the disease with increasing arsenic dose was observed.

Some studies have suggested that long-term exposure to arsenic can cause neurological problems. Cases of occupational arsenic polyneuropathy have been reported in copper refinery workers and workers in Japan involved in the desulphurisation of coal gas. In another study, an arsenic concentration of more than 0.05 mg/l in well-water at a site in Canada produced an excess of abnormal electromyelographic profiles in exposed people, relative to controls. In Czechoslovakia, a study of children living near a power plant burning local coal with a high arsenic content showed that they had significant hearing losses compared with a control group. However, a similar study carried out near a copper smelter in the USA did not find any significant effects. Another study in the USA examined the electromyelographic profiles of people living in an area with a high content of arsenic in the well-water. Of people using water with an arsenic content of at least 0.1 mg/l, 50% exhibited abnormal electromyelographic profiles (WHO, 1981).

Long-term exposure to inorganic arsenic has been implicated in disturbances of the haematopoietic system, including disturbed erythropoiesis and granulocytopenia.

2.4.3 CARCINOGENIC EFFECTS

Arsenic is currently classified as a Group 1 compound (carcinogenic to humans) by IARC (IARC, 1987), with most of the evidence for this linked to skin and respiratory cancers. IARC (1980) and Bates *et al.* (1992) stated that evidence for the causation of cancers, other than those of the lung and skin, is still open to debate.

The key available evidence relating to arsenic exposure is summarised in the following sections. Table 2.4.1 shows selected studies relating to carcinogenic effects following exposure to arsenic.

The WHO (1987) calculated that at an air concentration of 1 µg arsenic per m^3, a conservative estimate of lifetime risk is 3×10^{-3}. EPA risk estimates for carcinogenicity are given by IRIS, based on extrapolations using a time- and dose-related formulation of the multistage model; the arsenic levels in drinking water and air that correspond to an estimated cancer risk of 1 in 10^{-6} are 2×10^{-2} µg/l and 2×10^{-4} µg/m^3 respectively.

CARCINOGENIC EFFECTS FOLLOWING MEDICINAL EXPOSURE

Fowler's solution, which contains 1% potassium arsenite, has been used in the past to treat a variety of conditions including skin diseases. Its association with skin cancer has been confirmed (IARC, 1980). The concurrence of chronic arsenicism with invasive carcinomas of the skin has been reviewed by several authors. Characteristically these skin cancers were multifocal, involved areas of the body unexposed to sunlight and occurred at atypical sites such as the palms and soles, in contrast to cancers induced by sunlight, X-rays or radium. A series of reports also indicates an association between treatment with Fowler's solution and hepatic angiosarcoma; however, Bates *et al.* (1992) stated that the link remains tentative.

CARCINOGENIC EFFECTS FOLLOWING EXPOSURE *VIA* DRINKING WATER

Bates *et al.* (1992) and IARC (1980) reviewed studies of arsenic in drinking water, and in particular those concerned with the contamination of artesian wells in south west Taiwan. Clear dose–response relations were shown for arsenic in well-water and cancer of the skin, liver, lung, bladder and kidneys.

Tsuda *et al.* (1995) showed elevated standard mortality ratios for lung cancer and urinary tract cancer in an area of Japan with arsenic-contaminated well-water compared with a control group. They also showed some evidence of synergism between ingested arsenic exposure and smoking in the development of lung cancer.

Table 2.4.1. Selected arsenic studies with estimates of exposure and associated human carcinogenic endpoints

Study	Exposure estimate	Effect	Comments	Review
Medical treatment (Fowler's solution)				
Epidemiological n = 478	1% potassium arsenite	Bladder cancer Respiratory cancer	SMR (bladder cancer) = 2.5; SMR (respiratory cancer) = 0.8–1.8 Association tentative	Bates *et al.* (1992)
Epidemiological/ case histories n = 168	'Prolonged use' of 1% potassium arsenite	Hepatic angiosarcoma	Association tentative	Bates *et al.* (1992)
Epidemiological/ case histories n = 143	Mean dose = 28 g (0.2–121 g) 90% >1 year; 60% >5 years	Invasive carcinoma of skin	Association confirmed	IARC (1980)
Epidemiological/ case histories n = 262	Dose range = 0.1–26 g	Skin cancer	Dose–response shown Association confirmed	IARC (1980)
Contaminated drinking water (artesian wells)				
Epidemiological Taiwan	0.01–1.82 mg/l	Skin cancer	Dose–response shown Association confirmed	Bates *et al.* (1992)
Epidemiological Taiwan	0.01–1.8 mg/l for >60 years	Skin cancer	Dose–response shown	IARC (1980)
Epidemiological n = 113 Japan	>1 ppm for 5 years	Lung cancer Urinary tract cancer	SMR (lung cancer) = 15.69; SMR (urinary tract cancer) = 31.18	Tsuda *et al.*(1995)

Data from WHO (1992)

SMR, standard mortality ratio

CARCINOGENIC EFFECTS FOLLOWING OCCUPATIONAL EXPOSURE

Bates *et al.* (1992) reviewed several studies on the occurrence of cancers in German vine growers and the growers' associated exposure to arsenic. German investigators stated that the cause of the arsenic poisoning was the consumption of *Haustrunk* ('house drink'), a wine substitute made from an aqueous infusion of already-pressed grape skins and containing 2–90 mg/l of arsenic trioxide. Insecticides containing arsenic trioxide were widely used in vineyards until 1942. Many of the studies are hampered by confounding factors, but overall they suggest that arsenic ingestion is a cause of cancer of the lung and possibly other sites.

Several studies on copper smelter workers have demonstrated a significantly increased risk of respiratory cancers (IARC, 1980; Magos, 1991). The smelter workers are exposed to a range of carcinogens in addition to arsenic. In at least two studies attempts were made to control for SO_2 and in one of these copper, lead, nickel, selenium, antimony and bismuth were also considered; in both cases the excess of lung cancer remained. In one study of Swedish copper smelter workers the combined effects of smoking and arsenic exposure on lung cancer were intermediate between additive and multiplicative, and appeared less pronounced in heavy smokers (Järup & Pershagen, 1991).

An excess of lymphomas has been reported in workers manufacturing arsenic pesticide, and excesses of leukaemia, myeloma and colon and liver cancer have been found in smelter workers. An excess of oral cancers has been reported in a population exposed during the spinning of wool that may have been contaminated with arsenical sheep-dip (IARC, 1980). IARC, however, concluded that there was insufficient evidence that arsenic caused cancer at sites other than the lungs and skin.

A number of epidemiological studies of occupational exposure and cancer incidence have shown dose–response effects (Hertz-Picciotto & Smith, 1993). There is great variation in response between studies; in three smelter studies cumulative doses in the range of 4–15 mg/m^3 induced a two- to four-fold increase, whilst similar exposures were associated with a 20-fold increase in lung cancer risk among miners in China and a four- to seven-fold increase among insecticide manufacturing workers. The variation between these studies remains enigmatic; underestimation of exposure, interactions with carcinogenic exposures (e.g. nickel) and a differing proportion of susceptible individuals are the most likely explanations.

2.4.4 EXPOSURE LIMITS AND GUIDELINES

The WHO air quality guidelines document (WHO, 1987) states that "because arsenic is carcinogenic and there is no known safe threshold, no safe level…can be recommended".

The EPA's RfD value for hyperpigmentation, keratosis and possible complications of the vascular system is 0.3 µg/kg body weight/day, although this has an inherent uncertainty of perhaps an order of magnitude (IRIS, 1996).

Table 2.4.2 shows the exposure limits and guidelines set by various agencies for arsenic.

Table 2.4.2 Exposure limits and guidelines for arsenic

Agency	Form of arsenic	Exposure limit/guideline	References
HSE	Arsenic (excluding arsine)	0.1 mg/m^3 (MEL; 8-hr TWA RP)	HSE, 1996
	Arsine	0.2 mg/m^3 (OES; 8-hr TWA RP)	"
EPA	Arsenic	0.3 µg/kg bw/day (RfD)[a]	IRIS, 1996
	Arsenic in drinking water	50 µg/l (0.05 ppm)	ATSDR, 1993
OSHA	Arsenic	10 µg/m^3	ATSDR ,1993
JECFA	Inorganic arsenic	2.0 µg/kg bw/day (PMTDI) 15 µg/kg bw/week (PTWI)	JECFA, 1989

[a] For hyperpigmentation, keratosis and complications of the vascular system

PMTI, provisional maximum tolerable daily intake; PTWI, provisional tolerable weekly intake; RP, reference period

2.4.5 SUMMARY

Inorganic arsenic causes both acute and chronic toxicity in a number of organs including the respiratory tract, skin, liver, and peripheral nervous system. However, the major health effect of concern is its carcinogenicity. This occurs following long-term ingestion or inhalation; the main target organs are the skin and the lungs. Environmental exposure to arsenic is likely to constitute a very small cancer risk.

2.4.6 REFERENCES

ATSDR (1993) *ToxFAQs for arsenic*, Agency for Toxic Substances and Disease Registry, US Department of Human and Health Services

Bates, M.N., Smith, A.H. & Hopenhayn-Rich, C. (1992) Arsenic ingestion and internal cancers: a review. *Am. J. Epidemiol.*, *135*, 462–476

Hertz-Picciotto, I. & Smith, A.H. (1993) Observations on the dose–response curve for arsenic exposure and lung cancer. *Scand. J. Work Environ. Health*, *19*, 217–226

HSE (1996) *Occupational exposure limits 1996 (*Health and Safety Executive *EH40/96)*, Sudbury, UK, HSE Books

IARC (1980) *IARC monographs on the evaluation of carcinogenic risk of chemicals to humans*, Vol 23, *Some metals and metallic compounds*, Lyon, France, International Agency for Research on Cancer, pp 39–142

IARC (1987) *IARC monographs on the evaluation of carcinogenic risks to humans*, Supplement 7, *Overall evaluations of carcinogenicity: an updating of IARC Monographs Volumes 1–42*, Lyon, France, International Agency for Research on Cancer pp 100–103

IRIS (1996) *Integrated risk assessment system, nickel*, US Environmental Protection Agency, online search conducted January 1996

Järup, L. & Pershagen, G. (1991) Arsenic exposure, smoking and lung cancer in smelter workers — a case–control study. *Am. J. Epidemiol.*, *134*, 545–551

JECFA (1989) *Evaluation of certain food additives as contaminants* (Joint FAO/WHO Expert Committee on Food Additives, Technical Report 776), Geneva, Switzerland, World Health Organization

Magos, L. (1991) Epidemiology and experimental aspects of metal carcinogenesis: physiochemical properties, kinetics, and the active species. *Environ. Health Perspect.*, *95*, 157–189

NRCC (1978) *Effects of arsenic in the Canadian environment* (Publication No. NRCC 15391), Ottawa, Canada, National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality

Tsuda, T., Babazono, A., Yamamoto, E., Kurumatani, N., Mino, Y., Ogawa, T., Kishi, Y. & Aoyama, H. (1995) Ingested arsenic and internal cancer: a historical cohort study followed for 33 years. *Am. J Epidemiol.*, *141*, 198–209

WHO (1981) *Arsenic* (International Programme on Chemical Safety, Environmental Health Criteria, 18), Geneva, Switzerland, World Health Organization

WHO (1987) *Air quality guidelines for Europe* (European Series No. 23), Copenhagen, Denmark, World Health Organization

WHO (1992) *Inorganic arsenic compounds other than arsine* (Health and Safety Guide No. 70), Geneva, Switzerland, World Health Organization

2.5 CHROMIUM

2.5.1 INTRODUCTION

Chromium is a multivalent metal distributed widely throughout the biosphere. It is most commonly found in the trivalent state as metallic ores, but the hexavalent form is also present in the environment. Industrially, chromium is used in a number of processes including the manufacture of chromic acid, chromium pigments, leather tanning and corrosion control (WHO, 1988).

Chromium (III) is an essential trace element which is believed to play a physiological role in the metabolism of glucose. It has also been implicated in maintaining a healthy cardiovascular system in humans (WHO, 1988). Hexavalent chromium, on the other hand, is a multi-organ toxicant which induces a wide spectrum of both acute and chronic disorders (WHO, 1987; Baruthio, 1991). Because of its lower toxic potential, trivalent chromium has not received as much attention in the scientific literature as chromium (VI); few studies have discerned any possible long-term effect of chromium (III) in the absence of chromium (VI).

The toxicokinetics of chromium depend largely on the species involved. Chromium (VI) is absorbed by the lungs, the gastrointestinal tract and to some extent by intact skin; conversely, trivalent chromium is poorly absorbed by all routes (Lauwerys & Hoet, 1993). Only 5% of either respiratory or dietary chromium reaches the bloodstream (WHO, 1987); this amounts to a total daily intake by both routes combined of 50–200 µg (WHO, 1988). The gastrointestinal absorption of chromium may be reduced in the presence of zinc, which can antagonise chromium uptake (Baruthio, 1991).

Both trivalent and insoluble hexavalent chromium compounds are retained in the lung. Following absorption, chromium (III) is distributed by the blood to other tissues, particularly the liver, spleen and bone marrow, where it is retained. Hexavalent chromium, on the other hand, is rapidly eliminated in urine (Lauwerys

& Hoet, 1993). Concentrations of chromium in neonatal tissues are greater than the levels found in later life, but available data on possible fetotoxicity are limited (WHO, 1987). Chromium levels in children decline up to about ten years of age, after which there is an increase in the lung tissue concentration but a decrease in levels in other tissues. Long-term bioaccumulation is not a problem as tissue levels of chromium appear to decrease with age (the estimated whole-body half-life is 22 days for chromium (VI) and 92 days for chromium (III)). However, concentrations of chromium in the lungs seem to increase throughout life.

Although ingestion is the major route of exposure to chromium for the general public, most of the available data relate to respiratory exposure, particularly occupational exposures.

As an example of the general background level of chromium in air, the average mean annual level measured at five sites in the UK in 1990 was 0.0036 µg/m^3 (see Table 2.12.1). Assuming that 20 m^3 of air is breathed by an individual per day and that 5% of the inhaled chromium dose is absorbed (see above), this equates to an intake of approximately 0.072 µg/person/day. The total upper bound intake of chromium in the diet has been estimated to be 250 µg/person/day (see Table 2.12.1).

2.5.2 NON-CARCINOGENIC EFFECTS

Chromium salts and oxides are both irritant and corrosive. The acute toxic effects of these chromium compounds generally only occur at high levels; people exposed at work are therefore most prone to such effects. The dose–response relationships for the long-term effects of chromium have been difficult to establish, and again it is amongst those exposed occupationally that the impact of long-term exposure has been most extensively studied.

ACUTE TOXICITY

Short-term exposure to chromium is known to cause acute irritative dermatitis, as well as gastrointestinal disturbances after ingestion of high doses. Concentrated chromic acid solutions used in industry are highly corrosive. Slight effects on the respiratory tract have been reported to occur at levels of hexavalent chromium (as chromic acid) above 2 µg/m^3 (Lindberg & Hedenstierna, 1983).

CHRONIC TOXICITY

Both hexavalent and trivalent chromium are haptenic and are therefore capable of inducing immune responses at sites of contact. Skin contact can lead to allergic contact dermatitis, whilst respiratory sensitisation to hexavalent compounds can evoke an asthmatic response (WHO, 1987). Using patch tests, the threshold concentration for skin hypersensitisation to hexavalent chromium has been calculated as 10 mg/kg. The corresponding figure for trivalent chromium is almost 50 times higher, at around 500 mg/kg (Bagdon & Hazen, 1991).

Exposure to chromium by inhalation is also known to cause ulceration and perforation of the nasal septum (WHO, 1987). In a study of chrome plating workers, Lindberg & Hedenstierna (1983) reported a high incidence of nasal septal ulceration and perforation in subjects exposed to peak levels of 20–46 $\mu g/m^3$ chromic acid or more (8-hr mean exposure 2 $\mu g/m^3$ or more, exposure period ranged from 0.2–23.6 years). Renal effects have also been noted in workers exposed to chromium; increased urinary $ß_2$ microglobulin levels were seen in workers at a chromium plating plant with 8-hour time-weighted average chromium (VI) exposures of 2–20 $\mu g/m^3$ (HSE, 1989).

HEALTH EFFECTS FROM OCCUPATIONAL EXPOSURE

Workplaces are more likely to be contaminated by trivalent chromium than by the more toxic hexavalent form. A large number of occupational studies have documented some of the health effects described above, as summarised by WHO (1988).

HEALTH EFFECTS FROM ENVIRONMENTAL EXPOSURE

Available data on exposure to the general public are limited. Bagdon and Hazen (1991) reported a notable Japanese longitudinal survey of the general public carried out to study the long-term health effects of living in contaminated areas by Tokyo Metropolitan Government Bureau of Sanitation. The results suggested that the nephrotoxic effects of chromium may be important at long-term low levels of exposure. It was also noted that subjects in contaminated regions had an overall increase in contact dermatitis and eczema during the summer but not during the winter. This seasonal trend is consistent with observations that sunlight or short-wavelength light potentiates existing chromium-induced dermatitis (Bagdon & Hazen, 1991).

2.5.3 CARCINOGENIC EFFECTS

IARC has classified chromium (VI) as carcinogenic to humans (Group 1; IARC, 1990). The EPA has classified chromium (VI) as a human carcinogen (Group A; IRIS, 1996). IARC (1990) was unable to classify metallic chromium and chromium (III) compounds as to their carcinogenicity to humans (Group 3).

The lungs are particularly important in the toxicity of chromium, not only because they are one of the major sites of absorption and accumulation but because they are also the target organ for carcinogenesis. Epidemiologists have had to rely on occupational exposure data to identify and evaluate the carcinogenic risk that chromium poses to human health. WHO (1988) reported that people living near ferro-alloy plants and exposed to chromium concentrations in ambient air of up to 1 µg/m^3 showed no increased mortality from lung cancer. However, occupational studies (summarised in Table 2.5.1) have reported increased lifetime risks for lung cancer at chromium levels of 1 µg/m^3. A lifetime exposure to 1 µg/m^3 chromium (VI) was defined as posing a lifetime risk of 4×10^{-2} (WHO, 1987).

Table 2.5.1 Exposure risk estimates for chromium (VI) in epidemiological studies

Study	Site/population	Chromium exposure levels (µg/m^3)	Average lifetime exposure (µg/m^3)	Relative risk	Lifetime risk (associated with exposure to 1 µg/m^3)
A	Chromium metal production workers (two cohorts studied)	0.67[a] 0.37[a]	2 11.4	1.75 3.04	1.5×10^{-2} 7.2×10^{-3} (mean value: 1.1×10^{-2})
B	Ferrochrome plant workers in Norway	0.53[b]	6.9	8.5	4.3×10^{-2}
C	Chromate workers in Norway	0.5	11	38	1.3×10^{-1}

From WHO (1987)

[a] Cumulative exposure (µg/m^3 • year)

[b] The risk values have been calculated assuming chromium (VI) makes up 19% of this value

WHO (1987) considered three occupational studies in assessing the risk of chromium exposure to human health (Table 2.5.1). One study (A) was conducted on metallic chromium production workers. Several cohorts were investigated for the cumulative effects of chromium, and the relative risks of developing lung cancer were calculated from observed and expected cases.

The relative risk in study (B) was calculated by comparing exposed workers with non-exposed workers at the same plant. The chromium concentration was given as total chromium, that is with no distinction between the trivalent and hexavalent forms. It was assumed that 19% of the overall chromium content was chromium (VI) although the authors did not state the reasoning behind this figure. The actual level that workers were exposed to was unknown at the time the study was conducted; the value given in Table 2.5.1 (0.53 $\mu g/m^3$) was a mean value obtained in 1975, some five years before the study was conducted. The calculation presented in this study should therefore be considered an estimate.

Study (C) was based on the incidence of bronchial cancer in occupationally-exposed chromate workers, with the male Norwegian population being used as a control. It was suggested that the very high lifetime risk obtained (1.3×10^{-1}) may have been due to the small size of the working population (WHO, 1987).

Based on the epidemiological data presented in Table 2.5.1, lifetime risks for developing cancer varied from 1.3×10^{-1} to 1.1×10^{-2}, the geometric mean being 4.0×10^{-2} for exposure to 1 $\mu g/m^3$. Using other studies and different modelling techniques the EPA has calculated a similar figure, 1.2×10^{-2}, for the lifetime risk of developing cancer from exposure to 1 $\mu g/m^3$ of chromium (WHO, 1987). As mentioned above, the 1990 average mean annual concentration of chromium in air at five sites in the UK was 0.0036 $\mu g/m^3$.

2.5.4 EXPOSURE LIMITS AND GUIDELINES

As reviewed by Malsch *et al.* (1994), a number of inhalation reference concentrations (RfCs) for chromium have been used to estimate the risk of non-carcinogenic health effects. RfCs represent "an estimate (with uncertainty spanning perhaps an order of magnitude) of continuous exposure to the human

population (including sensitive sub-populations) that is likely to be without appreciable risk of deleterious effects during a lifetime".

In 1991 the EPA proposed an RfC of 0.002 µg/m^3 for both Cr (VI) and Cr (III). This value was based on a study which reported the occurrence of nasal mucosal atrophy in chrome-plating workers exposed to Cr (VI) mists. A LOAEL of 2.0 µg/m^3 identified in this study was adjusted for discontinuous exposure and divided by a cumulative uncertainty factor of 300 to arrive at the RfC. Other reports reviewed by Malsch *et al.* (1994) have argued that separate RfCs should be established for different valence states as well as for different forms, such as particulates and acid mists. Using this approach, RfCs of 1.2 µg/m^3 and 0.12 µg/m^3 have been calculated for Cr (VI) particulate and Cr (VI) acidic mists respectively. Malsch *et al.* (1994) have proposed a new method for calculating RfCs.

In setting air quality guidelines for Europe the WHO did not set a permissible level for chromium, on the basis that there is no carcinogenic threshold.

In contrast, Jones (1990) argued the possible existence of a carcinogenic threshold greater than the existing US threshold limit value (TLV). His reasoning was based on existing kinetic and metabolic information for chromium (III) and (VI). Based on metabolism data, pharmacokinetics and mechanisms of cancer induction, it has been suggested that carcinogenic chromium (VI) is completely reduced to non-carcinogenic chromium (III) at a level of approximately 1 mg/m^3 or less (Jones, 1990).

With regard to safety limits, both the US and UK governments have set similar standards. Table 2.5.2 shows the exposure limits and guidelines set by UK and US government agencies for chromium.

Table 2.5.2 Exposure limits and guidelines for chromium

Agency	Form of chromium	Exposure limit/guideline	Reference
HSE	Cr (III)	500 µg/m^3 (OES; 8-hr TWA RP)	HSE, 1996
	Cr (VI)	50 µg/m^3 (MEL; 8-hr TWA RP)	"
EPA	Cr (III) and (IV)	0.002 µg/m^3 (RfC)[a]	Malsch *et al.*, 1994
	Chromium (III) and (VI) in drinking water	100 µg/l	ASTDR, 1993
OSHA	Metallic chromium and insoluble salts	1000 µg/m^3 (TLV; 8-hr TWA RP)	OSHA, 1990
	Cr (II) and (III) soluble salts	500 µg/m^3 (TLV; 8-hr TWA RP)	"
	Cr (VI) and chromic acid	100 µg/m^3 (TLV; 8-hr TWA RP)	"
NIOSH[b]	Metallic chromium, Cr (II) and Cr (III)	500 µg/m^3 (10-hr day, 40-hr week)	ASTDR, 1993
	Cr (VI)	1 µg/m^3	"

[a] Based on nasal mucosal atrophy
[b] National Institute for Occupational Safety and Health

RP, reference period; TLV, threshold limit value

2.5.5 SUMMARY

The main health effects of exposure to chromium at occupational levels include damage to the nasal septum, dermatitis and lung cancer. Current occupational exposure limits protect against nasal changes, and personal hygiene (skin care) protects against dermatitis. Lung cancer is the health effect of concern at environmental exposure levels.

A lung cancer risk of 4×10^{-2} has been attributed to a lifetime exposure level of 1 µg/m^3. Measured levels of chromium in the UK are approximately 300-fold lower than this. The resulting risk from ambient exposure can be determined by the shape of the dose–response curve, but is likely to be significantly lower than 4×10^{-2}.

2.5.6 REFERENCES

ATSDR (1993) *ToxFAQs for chromium*, Agency for Toxic Substances and Disease Registry, US Department of Human and Health Services

Bagdon R.E. & Hazen R.E. (1991) Skin permeation and cutaneous hypersensitivity as a basis for making risk assessments of chromium as a soil contaminant. *Environ. Health Perspect.*, *92*, 111–119

Baruthio F. (1991) Toxic effects of chromium and its compounds. *Biol. Trace Element Res. 32*, 145–153

HSE (1989) *The toxicity of chromium and inorganic chromium compounds* (Health and Safety Executive Toxicity Review 21), London, UK, HMSO

HSE (1996) *Occupational exposure limits 1996* (Health and Safety Executive EH40/96), HSE, Sudbury, UK, HSE Books

IARC (1990) *IARC monographs on the evaluation of carcinogenic risks to humans*, Vol 49, *Chromium, nickel and welding*, Lyon, France, International Agency for Research on Cancer

Jones R. (1990) Hexavalent chrome: Threshold concept for carcinogenicity. *Biomed. Environ. Sci.*, *3*, 20–34

Lauwerys R.R. & Hoet P. (1993) *Industrial Chemical Exposure: Guidelines for Biological Monitoring*, (Second Edition), London, UK, Lewis Publishers

Lindberg E. & Hedenstierna G. (1983) *Chrome plating: symptoms, findings in the upper airways, and effects on lung function*, Arch. Environ. Health, *38*, *367–374*

Malsch P.A., Proctor D.M. & Finley B.L. (1994) Estimation of chromium inhalation reference concentration using the benchmark dose method: a case study. *Regulat. Toxicol. Pharmacol.*, *20*, *58–82*

OSHA (1990) *Title 29 Code of Federal Regulations* (Part 1910.0000), Washington DC, USA, US Department of Labor

WHO (1987) *Air quality guidelines for Europe* (European Series No. 23), Copenhagen, Denmark, World Health Organization

WHO (1988) *Chromium* (International Programme on Chemical Safety, Environmental Health Criteria, 61), Geneva, Switzerland, World Health Organization

2.6 NICKEL

2.6.1 INTRODUCTION

Nickel is a ubiquitous trace metal found in air, soil and water. While nickel has been shown to be an essential element for several animal species, nickel deficiency has never been demonstrated in humans and the human requirement for nickel is probably very low. Diet represents the major source of exposure, although absorption can also occur *via* inhalation or through the skin (percutaneously).

When nickel is ingested only a small proportion is absorbed through the gut. However, the level of absorption is related to the solubility of the nickel compound, and generally follows the relationship: nickel carbonyl > soluble nickel compounds > insoluble nickel compounds (WHO,1991). When nickel is ingested as nickel sulphate in drinking water about 25% is absorbed, compared with only 1% when it is ingested in food (Sunderman *et al.*, 1989).

The fraction of nickel absorbed from smoking and air inhalation may be as much as 50% and 100% respectively (WHO, 1987). When considering absorption *via* inhalation, the rate will depend on the solubility of the compound; soluble compounds will be rapidly absorbed while poorly soluble compounds will lead to lower rates but more prolonged absorption. Respiratory absorption and secondary gastrointestinal absorption are the major routes of occupational exposure. Percutaneous exposure is quantitatively negligible, but is important in the development of contact hypersensitivity.

Nickel carbonyl is the most acutely toxic nickel compound (WHO, 1991). However, it is relatively unstable in ambient air and there is little likelihood of exposure at, for example, hazardous waste sites (ATSDR, 1996). Information on the human health effects of other nickel compounds comes mainly from occupational exposure, principally in the nickel industry. Patch testing for nickel sensitivity has been carried out in the general population. The main human health

effects of nickel, including those known to occur at low-level exposure, are outlined below.

As an example of background levels of nickel in air, the average mean annual level measured at five sites in the UK in 1990 was 0.0012 µg/m^3 (see Table 2.12.1). Assuming that 20 m^3 of air is breathed by an individual per day and that 100% (worst case) of the inhaled nickel dose is absorbed, this equates to an intake of approximately 0.024 µg/person/day. The total upper bound intake of nickel in the diet has been estimated to be 170 µg/person/day (see Table 2.12.1).

2.6.2 NON-CARCINOGENIC EFFECTS

ACUTE TOXICITY

Nickel carbonyl is a volatile liquid that represents a major acute risk to human health in the workplace. Exposure to other nickel compounds is a minor risk in terms of acute effects. Information on the acute affects of these other nickel compounds is limited and generally restricted to accidental poisoning, particularly at work. In one incident, for example, 32 workers in an electroplating plant accidentally drank water contaminated with nickel sulphate and nickel chloride; 20 of them rapidly developed symptoms (nausea, vomiting, abdominal discomfort, diarrhoea, giddiness, lassitude, headache, cough, shortness of breath) that lasted for up to two days in some cases. The nickel doses received were estimated to range from 0.5–2.5 g (WHO, 1991).

CHRONIC TOXICITY AND OTHER EFFECTS

The major chronic effects of nickel exposure in humans are on the respiratory system and skin. Oral exposure at higher than environmental levels has also resulted in gastrointestinal effects (nausea, cramps, diarrhoea, vomiting), haematological effects (increased number of reticulocytes), hepatic effects (increase in serum bilirubin), neurological effects (giddiness, weariness) and renal effects (WHO, 1991; ATSDR, 1996).

The effects of nickel on the respiratory system have mainly been recorded in the occupational environment. In one study there was an elevated number of deaths from respiratory illness in nickel workers chronically exposed to concentrations of 0.04 mg nickel/m^3 or higher, usually in the form of nickel oxide or nickel sulphide (ATSDR, 1996). Other respiratory effects associated with chronic nickel exposure include chronic bronchitis, emphysema and reduced vital capacity; however, the workers with these conditions were also exposed to other metals including uranium, iron, lead and chromium, so nickel may not have been the sole causative agent (ATSDR, 1996).

In one study, 302 nickel industry workers were exposed to nickel sulphate at a concentration of 0.02–4.5mg/m^3 for more than ten years. The respiratory conditions reported included chronic sinusitis (83%), nasal septal erosion (41%), and nasal septal perforation (5.6%). In another study, 24.5% of nickel refinery workers had pathological changes of the nasopharynx; exposure at the plant between 1966 and 1970 ranged from 0.035–1.65 mg/m^3. Pneumoconiosis of an interstitial type, together with bronchitis, has been detected in a number of workers in the nickel industry. Dust collected from the workrooms of nickel refineries has been shown to induce a similar condition in experimental animals. Dusts that were pure nickel suboxides (Ni_2O_3) were found to cause lung fibrosis (WHO, 1991). Evidence also exists for the induction of asthma following occupational exposure to nickel. This may be due to primary irritation or a true allergic response (ATSDR, 1996). Asthmatic lung disease in nickel-plating workers exposed to soluble nickel has been reported. In six workers, allergic asthma could be provoked by the inhalation of nickel sulphate and chromium sulphate aerosols. Specific IgE antibodies to these provocative agents have been revealed (WHO, 1991).

Nickel dermatitis is the most prevalent health effect of nickel exposure in the general population. Nickel dermatitis is more prevalent in women, owing to their increased skin contact with nickel-plated objects such as jewellery, buckles and zips (ATSDR, 1996). In a review on contact dermatitis, Basketter *et al.* (1993) described several studies presenting human dose–response data. In one study, 25 volunteers who were positive in patch tests were exposed to nickel sulphate on their upper backs at concentrations ranging from 0.012 mg/l (0.012 ppm) to 11 200 mg/l (11 200 ppm) nickel. Fourteen of them reacted to 112 mg/l (112 ppm) nickel and one produced a minimal reaction at 11 mg/l (11 ppm). In another study of nickel-allergic volunteers using patch testing, the minimum concentration of nickel sulphate eliciting a response was 5 mg/l (5 ppm).

Evidence of renal damage has been reported in nickel refinery workers and in people who drank water contaminated with nickel. Of 11 nickel workers who had urinary nickel levels above 100 µg/l, five had increased levels of urinary ß-2-microglobulin (>240 µg/l). In another group of ten workers who were hospitalised after drinking water containing nickel sulphate, nickel chloride and boric acid, three had a transient increase in urine albumin. These workers were exposed to an estimated dose of 7.1–35.7 mg nickel/kg (ATSDR, 1996).

In reviewing the toxicology of nickel, ATSDR (1996) found no studies in which human oral exposure to nickel produced respiratory, endocrine, reproductive or developmental effects. WHO (1991) reported that no data were available on the effects of nickel on human reproduction and development.

2.6.3 CARCINOGENIC EFFECTS

IARC (1987, 1990) classified nickel compounds as Group 1 (carcinogenic to humans) and metallic nickel as Group 2B (possibly carcinogenic to humans). There is sufficient evidence in humans for the carcinogenicity of nickel sulphate, and of the combinations of nickel sulphides and oxides encountered in the nickel refining industry (IARC, 1990). The EPA classified nickel refinery dust as carcinogenic to humans (Group A; IRIS, 1996).

Evidence for these classifications comes mainly from studies of nickel refinery workers, where cohort studies have demonstrated elevated risks for lung and nasal cancers. ATSDR (1996) concurred that epidemiological studies of workers exposed to nickel *via* the inhalation route have demonstrated a carcinogenic effect in the lung and nasal cavities. ATSDR (1996) also stated that interpretation of the studies was complicated by the fact that exposure was to impure nickel compounds which contained relatively high levels of other metals.

IARC (1987) and Languård (1994) noted that in some studies exposure to chromium was a confounding factor. In a re-analysis of most of the epidemiological studies of nickel workers it was found that lung and nasal cancers were related primarily to exposure to soluble nickel compounds at concentrations greater than 1 mg/m^3, and to exposure to less soluble compounds at concentrations greater than or equal to 10 mg/m^3 (primarily oxides and sulphides;

ATSDR, 1996). ATSDR (1996) found no studies on human carcinogenic effects associated with oral and dermal exposure.

WHO (1987) presented incremental unit risk estimates for lung cancer for a lifetime exposure to nickel of 1 µg/m^3 based on three epidemiological studies in Ontario (Canada), Clydach (Wales) and Kristiansand (Norway) of 1.5 x10^{-4}, 5.7 x10^{-4}, and 5.9 x10^{-4}, respectively. The calculations were made using the average relative risk model. From these three studies the WHO (1987) calculated a lifetime risk of 4 x10^{-4} at an air nickel concentration of 1 µg/m^3. The air concentration of nickel associated with a 1 in 10^6 lifetime risk level of contracting lung/nasal cancer is estimated by the EPA to be 4 ng/m^3 (4 x10^{-3} µg/m^3). This is based on an additive and multiplicative dose extrapolation method using data for nickel sulphide refinery workers (IRIS, 1996).

2.6.4 EXPOSURE LIMITS AND GUIDELINES

Because of nickel's carcinogenic properties the WHO (1987) was unable to recommend a safe level for nickel in air.

Table 2.6.1 shows the exposure limits and guidelines set by UK and US government agencies for nickel.

The oral RfD (EPA) for nickel is 20 µg/kg bw/day. This is based on a NOAEL identified in a study on rats, multiplied by an uncertainty factor of 300 to take account of interspecies extrapolation, protection of sensitive individuals and inadequacies in reproductive studies. This RfD may not, however, protect people who are already sensitised to nickel (ATSDR, 1996).

Table 2.6.1 Exposure limits and guidelines for nickel

Agency	Form of nickel	Exposure limit/guideline	Reference
HSE	Metallic nickel	0.5 mg/m^3 (MEL; 8-hr TWA RP)	HSE, 1996
	Soluble nickel compounds	0.1 mg/m^3 (MEL; 8-hr TWA RP)	"
	Insoluble nickel compounds	0.5 mg/m^3 (MEL; 8-hr TWA RP)	"
	Organic nickel compounds	1 mg/m^3 (OES; 8-hr TWA RP)	"
		3 mg/m^3 (OES; 15-min RP)	"
EPA	Soluble nickel compounds	20 µg/kg bw/day (RfD)	ATSDR, 1996
OSHA	Nickel compounds that dissolve easily in water	100 µg/m^3 (8-hr day, 40-hr week)	ATSDR, 1996
	Nickel compounds that do not dissolve easily in water	1 mg/m^3	"
NIOSH	Nickel compounds except nickel carbonyl compounds	15 µg/m^3	ATSDR, 1996

RP, reference period

2.6.5 SUMMARY

Although occupational and accidental exposures to nickel can cause respiratory, gastrointestinal and renal effects, the toxic property of most concern is the carcinogenicity of inorganic nickel compounds. Allergic sensitisation to nickel and its salts, particularly contact dermatitis, is also a recognised problem in both occupational situations and among some members of the general population exposed to nickel-containing jewellery or fastenings. Background dietary exposure in the UK to nickel is approximately one-tenth of the EPA oral RfD. Airborne levels in the UK (see Table 2.12.1) are approximately one-third of the concentration which the EPA estimates to give a 1 in 10^6 risk of lung or nasal cancer.

2.6.6 REFERENCES

ATSDR (1996) *Toxicological profile for nickel*, Atlanta, USA, Agency for Toxic Substances and Disease Registry

Basketter, D.A., Briatico-Vangosa, G., Kaestner, W., Lally, C. & Bontinck, W.J. (1993) Nickel, cobalt and chromium in consumer products: a role in allergic contact dermatitis? *Contact Dermat.*, *28*, 15–25

HSE (1996) *Occupational exposure limits 1996*, (Health and Safety Executive EH40/96), Sudbury, UK, HSE Books

IARC (1987) *IARC monographs on the evaluation of the carcinogenic risk to humans*, Supplement 7, *Overall evaluations of carcinogenicity: An updating of IARC monographs Volumes 1–42*, Lyon, France, International Agency for Research on Cancer

IARC (1990) *IARC monographs on the evaluation of carcinogenic risks to humans*, Vol 49, *Chromium, nickel and welding*, Lyon, France, International Agency for Research on Cancer

IRIS (1996) *Integrated risk assessment system, nickel*, US Environmental Protection Agency, online search conducted January 1996

Languård, S. (1994) Nickel-related cancer in welders. *Sci. Tot. Environ.*, *148*, 303–309

Sunderman, F.W. Jr, Hopfer, S.M., Sweeney, K.R., Marcus, A.H., Most, B.M. & Creason, J. (1989) Nickel absorption and kinetics in human volunteers. *Proc. Soc. Exp. Biol. Med.*, *191*, 5–11

WHO (1987) *Air quality guidelines for Europe* (European Series No. 23), Copenhagen, Denmark, World Health Organization

WHO (1991) *Nickel* (International Programme on Chemical Safety, Environmental Health Criteria, 108), Geneva, Switzerland, World Health Organization

2.7 DIOXINS

2.7.1 INTRODUCTION

Polychlorinated dibenzodioxins and furans (PCDD/Fs*, 'dioxins') are ubiquitous in the environment. Combustion processes are major sources of dioxins, and lead to their wide dispersal in the environment. Because dioxins are lipophilic they tend to accumulate in fatty tissue. The most highly chlorinated dioxins are found at the greatest concentrations. PCDD/Fs are very persistent: a half-life of 5.8–9.6 years has been reported for 2,3,7,8-TCDD, from studies on Vietnam veterans exposed to Agent Orange defoliants (Michalek *et al.*, 1992). The half-lives of other PCDD/Fs would be expected to increase with increasing level of chlorination.

The toxicity of a mixture of PCDD/Fs is commonly expressed as a 'toxic equivalent' (TEQ). This is a figure obtained by multiplying the concentration of individual dioxin species ('congeners') by a suitable toxic equivalent factor (TEF) and summing the results. TEF values are calculated relative to the most toxic congener, 2,3,7,8-TCDD, which is assigned a TEF of 1.

A mean background level of 1.4 ng/g fat (equivalent to 57 pg TEQ/g fat) has been reported for the sum of all 2,3,7,8-substituted PCDD/Fs in human adipose tissue in the Welsh population (Duarte-Davidson *et al.*, 1993). A mean level of 0.5 ng/g fat has been reported in two UK human milk samples, each pooled from 40 individual samples from breast-feeding mothers in two cities (DoE, 1989).

*In this paper 'dioxins' are taken to include the polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzo-*p*-furans (PCDFs). These PCDD/Fs are halogenated aromatic compounds substituted in several positions by one or more chlorine atoms. They are formed as trace by-products in processes involving chlorine and organic compounds. Of the 210 PCDD/Fs the best studied has been 2,3,7,8-tetrachlorodibenzodioxin (TCDD).

The major route of exposure to dioxins (over 95% of the typical daily intake) is food, especially meat, fish, and dairy products. Inhalation and drinking water are minor sources (French Academy of Sciences, 1995). Levels of dioxins in air have been measured at various sites in the UK, and in 1993 the total average level of 17 dioxin and furan congeners at four sites was 6.8 pg/m^3 (see Table 2.12.1). Assuming that 20 m^3 of air is breathed by an individual per day and that 100% (worst possible case) of the inhaled dioxin dose is absorbed, this equates to an intake of approximately 140 pg/person/day for these congeners (see Table 2.12.1).

The total daily intake of PCDD/Fs by the average UK consumer has declined from an estimated value of 240 pg TEQ/person/day in 1982 to 125 pg TEQ/person/day in 1988 and to 69 pg TEQ/person/day in 1992 (MAFF, 1995). These estimates represent 'upper bound' intakes as they were calculated assuming that compounds present at levels below the limit of detection (LOD) were actually present at the LOD, thereby overestimating daily intake. It has been estimated that exposure of populations in industrialised countries was 135 pg TEQ/person/day in late 1990 (French Academy of Sciences, 1995), which agrees with the decline reported above for the UK.

The reduction in daily intake of PCDD/Fs by the general population of the UK has been caused mainly by changes in dietary habits and a fall in the average fat content of many foodstuffs, rather than by a decline in environmental PCDD/F levels (MAFF, 1995).

There is a vast body of epidemiological information on the health effects of exposure to dioxins. The major reported effects include chloracne, diabetes, hormonal and developmental effects, immunological changes and some evidence of increased neoplastic disease. These effects have been reviewed by a number of authors and agencies (Tollefson, 1990; Gough, 1991; Houk, 1991; ATSDR, 1993; Schecter, 1994; Brouwer *et al.*, 1995; French Academy of Sciences, 1995).

2.7.2 NON-CARCINOGENIC EFFECTS

Several toxic effects occur in animals after exposure to PCDD/Fs, but many of these have not been observed in humans (Schecter, 1994). The toxicity of PCDD/Fs certainly varies significantly between species. The absence of a clear association between animal and human data may therefore be due to differences in susceptibility to PCDD/Fs, as well as the general lack of human data.

At present, evidence linking dioxin exposure to a number of human toxicological endpoints, including carcinogenic, neurological, immunotoxic, teratogenic and reproductive effects, is far from conclusive. Chloracne and transient hepatic changes are the only well-documented human health effects attributable to PCDD/F exposure (ATSDR, 1993).

The presence of the skin disease chloracne is a good indicator of exposure to high levels of PCDD/Fs, although it is not an inevitable result and similar polyhalogenated compounds can also cause chloracne (Houk, 1991). For example, in one study, among a subgroup of six individuals exposed at Seveso (see Section 2.7.3) four did not develop chloracne despite blood dioxin levels of 800–10 500 ppt, whereas two people with blood levels of 800 and 1700 ppt did develop the condition. (French Academy of Sciences, 1995). Of the estimated 35 000 people exposed to dioxins at Seveso, 193 (0.6% of the population) reported chloracne (Gough, 1991).

Transient changes in levels of hepatic enzymes have also been positively associated with dioxin exposure in humans (ATSDR, 1993). For example, levels of gamma glutamyl transpeptidase and alanine aminotransferase were elevated in Seveso children although no apparent impairment of liver function was found. The toxicological significance of these elevations is not clear, although elevated gamma glutamyl transpeptidase may suggest increased xenobiotic metabolism, whilst increased alanine aminotransferase is associated with more general liver damage.

Despite compelling evidence from studies in animals, human data demonstrate only an equivocal association between dioxin exposure and thyroid changes. Dioxins have been reported to have anti-oestrogenic activities in animals and humans. Increased levels of TCDD in serum have been correlated with increases in serum levels of follicle stimulating hormone and luteinising hormone, and decreases in levels of testosterone, in male workers manufacturing 2,4,5-trichlorophenol (Schecter, 1994; French Academy of Sciences, 1995).

Lack of data on the immunological effects of dioxins in humans has prevented any firm conclusions from being drawn on whether PCDD/Fs are immunotoxins. Studies to date have produced conflicting findings, with some showing positive correlations and others showing no link at all (ATSDR, 1993).

Although some studies have demonstrated acute neurological effects, the overall conclusion is that even high exposures to dioxins do not cause chronic non-carcinogenic effects in adults (ATSDR, 1993).

2.7.3 CARCINOGENIC EFFECTS

Studies in experimental animals indicate that dioxins are amongst the most potent carcinogens known (Gough, 1991); however, evidence linking PCDD/Fs with human cancers is equivocal (Tollefson, 1990). The major epidemiological studies that have examined exposure to dioxins and cancer have been critically reviewed by Gough (1991) and Tollefson (1990). According to these authors, most of the available epidemiological data provide little firm evidence that dioxins are carcinogenic.

However, recently the International Agency for Research on Cancer has evaluated TCDD as a Group 1 carcinogen (carcinogenic to humans) and polychlorinated dibenzofurans and dibenzo-*p*-dioxin as Group 3 (not classifiable as to their carcinogenicity in humans; IARC, 1997). The EPA has classified dioxins as a Group 2B carcinogen (a probable human carcinogen for which there is inadequate evidence or no data for carcinogenicity in humans but sufficient evidence in animals; Gough, 1991).

CARCINOGENIC EFFECTS FOLLOWING ACCIDENTAL EXPOSURE

In 1976 the population surrounding the ICMESA plant in Seveso, Italy, was exposed to high levels of dioxins following a chemical accident. Bertazzi *et al.* (1993) carried out a detailed study of the affected population. In one area (the R zone, situated furthest from the plant), the incidence of soft tissue sarcomas was significantly elevated in males ten years after the accident (relative risk = 2.8; 95% CI = 1.0–7.3). There was also an elevated risk of females developing hepatobiliary cancer (relative risk = 3.3; 95% CI = 1.3–8.1) in an area surrounding the plant.

Although this study is potentially useful in assessing cancer risks because of the likely high exposure levels, the small number of reported cases limits interpretation of the results. Also, considering the sometimes long latency of cancer, 10–12 years may not be a sufficiently long period over which to examine the full effects of exposure. In addition, the majority of those highly exposed were children or young adults at the time of the incident, and there is little evidence, from human or animal studies, to support the assumption that dioxin exposure increases the incidence of cancer in these age groups (Tollefson, 1990). The authors noted that soft tissue

sarcomas were commonest in the region of least exposure, and that there was no excess risk of cancer in the most polluted areas. However, the highest exposed subgroup was small and only a few cases of cancer were found (Bertazzi *et al.*, 1993).

CARCINOGENIC EFFECTS FOLLOWING EXPOSURE FROM MUNICIPAL WASTE INCINERATION

Nessel *et al.* (1991) assessed the cancer risk to humans from PCDD/Fs released from a municipal waste incinerator. The evaluation was based on a number of assumptions about:

- the fate and transport of PCDD/Fs;
- human exposure to the emissions; and
- low-dose extrapolation modelling from animal studies to derive a potency factor applicable to humans.

The upper bound lifetime cancer risk for TCDD was calculated for three possible scenarios: the population as a whole (lifetime risk 1.8×10^{-7}, total estimated exposure *via* all routes 0.0011 pg TEQ/kg bw/day), the highly exposed (lifetime risk 2.5×10^{-6}, total estimated exposure 0.0160 pg TEQ/kg bw/day) and a worst-case scenario (lifetime risk 6.7×10^{-6}, total estimated exposure 0.0432 pg TEQ/kg bw/day). The study concluded that these values were likely to be overestimates in view of the conservative initial assumptions, and that emissions from the incinerator were unlikely to constitute a significant public health burden.

CARCINOGENIC EFFECTS FOLLOWING OCCUPATIONAL EXPOSURE

Saracci *et al.* (1991) reported a historical cohort study of 18 910 production workers and sprayers from ten countries exposed to chlorophenoxy herbicides and chlorophenols. The study looked at all neoplasms — the most common epithelial cancers and lymphomas — and found no overall excess mortality. For soft tissue sarcomas a statistically significant excess risk was noted. Based on a small number of deaths there also appeared to be increased risks for developing cancer of the testis, thyroid and other endocrine glands, and of the nose and nasal cavities. This was linked to exposure to chlorophenoxy herbicides, but not specifically to those herbicides probably contaminated by TCDD.

The effects of spraying phenoxy herbicide preparations (in which dioxins are present as contaminants) was studied in two international nested case-control studies. The studied group was matched with controls for age, sex and country of residence. The neoplasms were identified from death certificates and histological diagnosis. An excess risk of soft tissue sarcomas was associated with exposure to PCDD/Fs (odds ratio = 5.6; 95% CI = 1.1–28) and to TCDD (odds ratio = 5.2; 95% CI = 0.85–32). In the second study, a weak association was found between non-Hodgkin's lymphoma and exposure to dioxins (Kogevinas *et al.*, 1995).

The National Institute for Occupational Safety and Health (NIOSH) maintains a registry of around 6000 workers involved in the production of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4,5-trichlorophenol (2,4,5-TCP) contaminated with dioxins. Because of the high levels of exposure and the long latency period, this study is potentially useful in risk assessment. However, the small number of subjects may make it difficult to distinguish between cancer incidence in the study group and background levels in the general population. Tollefson (1990) has calculated the maximum risk of developing cancer to be 4.5×10^{-4}. This is based on the assumption that the blood levels of TCDD were up to 30 000 ppt (on a lipid-weight basis) at the time of exposure and 2658 ppt at the time of termination of employment.

A recent retrospective cohort study looked at male chemical workers producing phenoxy herbicides known to be contaminated with TCDD (Flesch-Janys *et al.*, 1995). Estimates of PCDD/Fs found in adipose tissue and blood were used to investigate the link between mortality and exposure. The exposed group was divided into quintiles and deciles according to exposure estimates, and compared with a reference cohort of gas workers. Causes of death were established from medical and life insurance records, and by consulting doctors and relatives. The total mortality was elevated in all groups, with the highest risk being observed in the highest TCDD decile (relative risk = 2.43; 95% CI = 1.80–3.29). The highest relative risks for cancer (relative risk = 3.3; 95% CI = 2.05–5.31) and ischaemic heart disease (relative risk = 2.48; 95% CI = 1.32–4.66) were found in the highest PCDD/F exposure group. The findings of this study indicate a dose-dependent association between mortality due to cancer or ischaemic heart disease and PCDD/F exposure.

2.7.4 EXPOSURE LIMITS AND GUIDELINES

In setting an acceptable daily intake (ADI) for dioxins, a WHO panel used the lowest observed adverse effect level in animals based on carcinogenic, hepatotoxic, immunotoxic and reproductive toxicity endpoints. Based on a no effect level of 1000 pg/kg, a factor of 100 was applied to take into account toxicokinetic differences and the uncertainties regarding reproductive toxicity, giving a recommended value of 10 pg/kg bw (WHO, 1991).

The WHO level of 10 pg/kg bw/day (equivalent to 600 pg/person/day for a 60 kg individual) has subsequently been endorsed by the UK Committee on Toxicity of Chemicals in Food (COT) as a tolerable daily intake (COT, 1995). In approving this value the committee considered intake on any one day to be of limited significance, provided the average intake was not exceeded over a period of weeks or months. It therefore considered 10 pg/kg/day as a time-weighted average equivalent to, say, 70 pg/kg bw/week TCDD-equivalent (MAFF, 1992; 1995). As noted above (see page 70) the UK average mean intake of dioxins has fallen over the past decade to 69 pg TEQ/person/day (equal to approximately 1 pg TEQ/kg bw/day for a 70 kg person), which is one order of magnitude below the present TDI.

The EPA assumes TCDD to be a complete carcinogen and has used the linearised multi-stage model to estimate an ADI of 6.4 fg TCDD/kg bw/day. This value is derived from an animal carcinogenicity study, in which a no-effect-level of 1 ng/kg bw/day was observed (Safe, 1991).

It has been estimated that breastfed babies receive 100 pg TEQ/kg bw/day (RCEP, 1993), which exceeds recommended levels. Guidelines are set on the basis of protecting individuals from the chronic effects of accumulation of PCDD/Fs in the body. The period of breastfeeding is short compared with the long half-lives of these compounds; there is, therefore, insufficient time for the body burden of the babies to reflect this high intake (MAFF, 1992). The COT (1995) therefore encourages breastfeeding as the benefits outweigh any possible risks. Some studies have investigated possible adverse effects in breastfed babies, but confounding factors such as co-contamination with PCBs have prevented firm conclusions from being drawn.

In a recent review (ENVIRON, 1995) it was concluded that there was insufficient evidence to suggest that humans would experience adverse health effects at current body burdens of dioxins. COT has also recently reiterated its recommendations of 1989 and 1991: "…the most useful action which could be taken to reduce exposures to these undesirable compounds is, as far as possible, to identify the continuing major sources of PCDDs and related compounds and to take appropriate measures to reduce inputs to the environment in the long term, with the aim of reducing levels in food and human tissues" (COT, 1995).

Table 2.7.1 shows exposure limits and guidelines for dioxins set by various agencies.

Table 2.7.1 Exposure limits and guidelines for dioxins

Agency	Form of dioxins	Exposure limit/guideline	Reference
COT	2,3,7,8-TCDD	10 pg/kg bw/day (TDI)	COT, 1995
French Academy of Sciences	2,3,7,8- TCDD	10 pg/kg bw/day (ADI)	French Academy of Sciences, 1995
EPA	TCDD	6.4 fg/kg bw/day (TDI)	Safe, 1991
WHO	2,3,7,8-TCDD	10 pg/kg bw/day (TDI)	WHO, 1991

ADI, acceptable daily intake; TDI, tolerable daily intake

2.7.5 SUMMARY

As well as producing chloracne at high doses, exposure to dioxins may harm human metabolism, development and reproduction. These adverse impacts may occur at levels less than ten times the average background levels or body burdens. However, much uncertainty surrounds these health effects. Current evidence suggests that PCDD/Fs may present a cancer hazard to humans but this is by no means conclusive.

2.7.6 REFERENCES

ATSDR (1993) Dioxin toxicity. *Am. Fam. Physic.*, *47*, 855–861

Bertazzi, P.A., Pesatori, A.C., Consonni, D., Tironi, A., Landi, M.T. & Zocchetti, C. (1993) Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. *Epidemiol.*, *4*, 398–406

Brouwer, A., Alhborg, U.G., Van der Berg, M., Birnbaum, L.S., Boersma, E.R., Bosveld, B., Denison, M.S., Gray, L.E., Hagmar, L., Holene, E., Huisman, M., Jacobson, S.W., Jacobson, J.L., Koopman-Essebom, C., Koppe, J.G., Kulig, B.M., Morse, D.C., Muckle, G., Peterson, R.E., Sauer, P.J.J., Seegal, R.F., Smits-Van Prooije, A.E., Touwen, B.C.L., Weisglas-Kuperus, N. & Winneke, G. (1995) Functional aspects of developmental toxicity polyhalogenated aromatic hydrocarbons in experimental animals and human infants. *Eur. J. Pharmacol. Environ. Toxicol. Pharmacol.*, *293*, 1–40

COT (1995) *Statement by the committee on toxicity of chemicals in food, consumer products and the environment on the EPA draft health assessment document for 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds*, available from the Department of Health, Skipton House, 80 London Road, London

DoE (1989) *Report of an Interdepartmental Working Group on polychlorinated dibenzo-para-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs)* (Pollution Paper No.27), Department of the Environment, London, UK, HMSO

Duarte-Davidson, R., Harrad, S.J., Allen, S., Sewart, A. & Jones, K.C. (1993) The relative contribution of individual PCBs, PCDDs and PCDFs to toxic equivalent values derived for bulked human adipose tissue samples from Wales, United Kingdom. *Arch. Environ. Contam. Toxicol.*, *24*, 100–107

ENVIRON (1995) *An expert panel review of the US Environmental Protection Agency's draft risk characterisation of the potential health risks of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds*, available from the Science Advisory Board of the US Environmental Protection Agency, Washington DC, USA

Flesch-Janys, D., Berger, J., Gurn, P., Manz, A., Nagel, S., Waltsgott, H. & Dwyer, J. (1995) Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. *Am. J. Epidemiol.*, *142*, 1165–1175

French Academy of Sciences (1995) *Dioxin and its Analogues*, Comité des Applications de l'Academie des Sciences, Lavoisier Publishing

Gough, M. (1991) Human health effects: what the data indicate. *Sci. Tot. Environ.*, *104*, 129–158

Houk, V.N. (1991) The health effects of dioxin on humans. *Quality Assurance: Good Practice, Regulation, and Law*, *2*, 97–103

IARC (1997) *IARC monographs on the evaluation of carcinogenic risks to humans*, Vol 69, *Polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans,* Lyon, France, International Agency for Research on Cancer (in press)

Kogevinas, M., Kauppinen, T., Winkelmann, R., Becher, H., Bertazzi, P.A., Bueno-de-Mesquita, H.B., Coggon, D., Green, L., Johnson, E., Littorin, M., Lynge, E., Marlow, D.A., Mathews, J.D., Neuberger, M., Benn, T., Pannett, B., Pearce, N. & Saracci, R. (1995) Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols and dioxins: two nested case-control studies. *Epidemiology*, *6*, 396–402

MAFF (1992) *Dioxins in food* (Food Surveillance Paper No. 31*)*. Ministry of Agriculture, Fisheries and Food, London, UK, HMSO

MAFF (1995) *Dioxins in food-UK Dietary Intake* (Food Surveillance Information sheet No. 71). Ministry of Agriculture, Fisheries and Food, London, UK, HMSO

Michalek, J.E., Tripathi, R.C., Caudill, S.P. & Pirkle, J.L. (1992) Investigation of TCDD half-life heterogeneity in veterans of Operation Ranch Hand. *J. Toxicol. Environ. Health*, *35*, 29–38

Nessel, C.S., Butler, J.P., Post, G.B., Held, J.L., Gochfeld, M. & Gallo, M.A. (1991) Evaluation of the relative contribution of exposure routes in a health risk assessment of dioxin emissions from a municipal waste incinerator. *J. Exp. Anal. Environ. Epidemiol.*, *1*, 283–307

RCEP (1993) *Incineration of waste* (Royal Commission on Environmental Pollution, Seventeenth Report). London, UK, HMSO

Safe, S. (1991) Polychlorinated dibenzofurans: environmental impact, toxicology, and risk assessment. *Toxic Substances J.*, *11*, 177–222

Saracci, R., Kogevinas, M., Bertazzi, P.A., Bueno-de-Mesquita, B.H., Coggon, D., Green, L.M., Kauppinen, T., L'Abbe, K.A., Littorin, M., Lynge, E., Mathews, J.D. Neuberger, M., Osman, J., Pearce, N. & Winkelmann, R. (1991) Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet*, *338*, 1027–1032

Schecter, A. (1994) *Dioxins and Health*, London, UK, Plenum Press

Tollefson, L. (1990) Use of epidemiological data to assess the cancer risk of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Regulat. Toxicol. Pharmacol.*, *13*, 150–169

WHO (1991) *Consultation on tolerable daily intake from food of PCCDs and PCDFs*, Bilthoven, Netherlands, World Health Organization Regional Office for Europe

2.8 POLYCYCLIC AROMATIC HYDROCARBONS

2.8.1 INTRODUCTION

Polycyclic aromatic hydrocarbons (PAHs) form a group of highly lipophilic chemicals released during combustion processes, including natural fires. They also occur in fossil fuels. They are ubiquitous in the environment, often present in very small quantities — of the order of μg/m^3 or ng/m^3. Humans are usually exposed to PAHs as complex mixtures such as coal tar pitch, soot, creosote, tobacco smoke and diesel fume. These mixtures of PAHs are also likely to contain other known human carcinogens. Toxicological data for single PAHs are therefore available only from animal studies (IARC, 1983; ASTDR, 1995).

Benzo[*a*]pyrene (BaP) is the most studied PAH, and has been used as an indicator of general PAH exposure. However, it is not always a good indicator, as different types of combustion processes generate mixtures containing varying proportions of PAHs and other compounds in both the vapour and particulate phases (Ström *et al.*, 1993).

The average total daily intake of PAHs in the general population has been estimated to be about 0.2 μg/person from air and 0.16–1.6 μg/person from food (ASTDR, 1995); levels of PAHs are higher in foods that are grilled or smoked. Background levels of PAHs in the air and diet have been reported for the UK. The total average concentration of 15 PAH compounds (including BaP) measured at four sites in 1993 was 0.128 μg/m^3 (128 ng/m^3; see Table 2.1.2.1). The annual average level of BaP alone was 0.41 ng/m^3. Assuming that 20 m^3 of air is breathed by an individual per day and that 100% (worst case) of the inhaled PAH dose is absorbed, these figures equate to intakes of approximately 2.6 μg/person/day of total PAHs and 0.008 μg/person/day of BaP. Dennis *et al.* (1983) analysed a

number of food components of the UK diet for 11 PAHs (fluoranthene, pyrene, benzo[*a*]anthracene, chrysene, benzo[*e*]pyrene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, BaP, benzo[*g,h,i*]perylene, dibenzo[*a,h*]anthracene and indeno[1,2,3-*c,d*]pyrene). Based on estimates of the contributions of different food groups to the total diet, they estimated that the total dietary load of these PAHs was 3.7 µg/person/day.

2.8.2 NON-CARCINOGENIC EFFECTS

PAHs have low acute toxicity. Other more toxic agents that often occur in association with PAHs are probably responsible for any acute effects observed (ATSDR, 1993).

Several human health effects have been reported to be associated with long-term exposure to coal tar and its by-products. These include erythema, burns and warts on sun-exposed areas of the skin, irritation to and photosensitivity of the eyes, cough, bronchitis, and haematuria (ATSDR, 1993). PAHs may also affect the human fetus: animal studies have confirmed that PAH and metabolites cross the placenta. Animals exposed to PAH *in utero* show a decrease in the number of functional oocytes, often to the point of infertility (ATSDR, 1993).

Ström *et al.* (1993) reviewed the possible link between exposure to combustion products, including PAHs, and cardiovascular disease. The authors stated that animal studies in the laboratory using single PAHs strongly support the hypothesis that PAHs contribute to the development of atherosclerosis, a major underlying cause of cardiovascular disease. Human epidemiological evidence was considered to be limited and ambiguous. Several epidemiological studies, however, are thought to indicate an association between occupational exposure to combustion products (including PAHs) and mortality from cardiovascular disease. It was concluded that at least some PAHs have the ability to promote atherosclerosis. For a definitive evaluation concerning the effects of human PAH exposure, further epidemiological studies are necessary, with detailed exposure assessments of occupational as well as non-occupational exposures (Ström *et al.*, 1993).

2.8.3 CARCINOGENIC EFFECTS

Benz[*a*]anthracene, dibenz[*a,h*]anthracene and BaP are classified as Group 2A carcinogens (probably carcinogenic to humans) by IARC (1987). This category is used when there is limited evidence of carcinogenicity in humans but sufficient evidence of carcinogenicity in experimental animals. Several other PAHs are classified as Group 2B carcinogens (possibly carcinogenic to humans) or Group 3 (not classifiable; IARC, 1987).

Some, but not all, individual PAHs have been shown to be carcinogenic *via* dermal application, inhalation and implantation in a number of animal species. Because people are never exposed to single PAHs, evidence of human health effects comes from studies of populations exposed to chemical mixtures. Although this evidence is quite compelling, it is inferred rather than direct (IARC, 1983). The evidence suggests that PAHs cause cancer of the skin and respiratory organs, and perhaps also of the bladder and gastrointestinal tract. Some studies have shown synergy between occupational PAH exposure and smoking (IARC, 1984). The high levels of PAH-DNA and protein adducts found in populations with high PAH exposure and lung cancer risk is additional evidence for the role of PAHs in the development of lung cancer (Seto *et al.*, 1993; Mumford *et al.*, 1993).

Epidemiological studies have shown increased mortality from lung cancer in people exposed to coke-oven emissions, roofing-tar emissions and tobacco smoke. Each of these mixtures contains BaP, chrysene, benz[*a*]anthracene, benzo[*b*]fluoranthene, dibenz[*a,h*]anthracene and other potentially carcinogenic PAHs, as well as other carcinogens, co-carcinogens, tumour promoters and initiators, such as nitrosamines, coal tar pitch and creosote (ASTDR, 1995). Several studies of workers have shown an increased risk of skin and scrotal cancer after dermal exposure to soots, tars and mineral oils, and of lung cancer after dermal exposure to coal-gas emissions (IARC, 1983). In addition, epidemiological studies of PAH exposure have revealed an increased incidence of bladder and gastrointestinal cancers (ATSDR, 1993). These reports provide qualitative evidence of the potential for mixtures containing PAHs such as BaP, chrysene, benz[*a*]anthracene, benzo[*b*]fluoranthene and dibenz[*a,h*]anthracene to cause cancer in humans.

Gustavsson (1989) commented that there is now accumulating evidence that no single substance in combustion products can be considered a marker of

carcinogenic activity. Data from a study reviewed by Gustavsson (1989) indicated that neither total PAHs nor BaP seemed to be a marker for mutagenic activity in different combustion product mixtures. Nisbet & LaGoy (1992) reviewed data on the toxicity of PAHs and concluded that most were less toxic than BaP; risk assessments that assume the total PAHs present to be as toxic as BaP are therefore likely to overestimate the risk.

Stavric & Klassen (1994) reported that the general population receives more BaP from foods than from smoking. The authors conclude, however, that epidemiological studies have not implicated BaP from foods as a causative factor in human cancers. It is possible that dietary constituents play a role in reducing the absorption of BaP from the gut.

Nitro-PAHs are known to form in the atmosphere from PAHs. Some nitro-PAHs are potent bacterial mutagens, exhibit various genotoxic effects including formation of DNA adducts, and are carcinogenic to experimental animals. Although there is no definite link between nitro-PAHs and human cancer there is some limited evidence that engine exhausts, which contain significant amounts of these compounds, may be carcinogenic to humans (IARC, 1994).

The EPA has suggested an upper-bound lifetime cancer risk estimate for exposure to 1 μg/m^3 of benzene-soluble coke-oven emissions in ambient air of 62 per 100 000 exposed individuals. Assuming a 0.71% content of BaP in these emissions, it can be estimated that 9 out of 100 000 people exposed to 1 ng BaP/m^3 over a lifetime would be at risk of developing cancer (WHO, 1987).

2.8.4 EXPOSURE LIMITS AND GUIDELINES

Because of the evidence for carcinogenicity, WHO (1987) could not recommend a safe level for PAHs.

NIOSH has determined that workplace exposure to coal products can increase the risk of lung and skin cancer in workers, and suggests a workplace exposure limit for coal tar products of 0.1 mg PAH/m^3 of air for a 10-hour workday and 40-hour working week. NIOSH has not suggested a specific workplace limit for BaP.

Table 2.8.1 shows exposure limits and guidelines set by US government agencies for PAHs.

Table 2.8.1 Exposure limits and guidelines for PAHs

Agency	Form of PAHs	Exposure limit/guideline	Reference
EPA	BaP in drinking water	0.2µg/l*	ATSDR, 1993
OSHA	BaP	0.2mg/m^3	ATSDR, 1990
NIOSH	Total PAH (10-hr day, 40-hr week)	0.1 mg/m3	ATSDR, 1990

* Proposed

2.8.5 SUMMARY

Epidemiological evidence indicates elevated risks for lung, skin, and perhaps bladder and gastrointestinal cancers in certain groups of people exposed to mixtures containing PAHs, such as coke-oven workers and smokers. Animal experiments on individual PAHs have shown some to be carcinogenic. IARC has classified a number of PAHs as "probably carcinogenic to humans" on this basis. Because PAHs form a heterogenous group of compounds and no two sources are likely to contain the same number or levels of compounds, it is not considered possible here to give a general estimate of risk from environmental exposure.

2.8.6 REFERENCES

ATSDR (1990) *Public health statement for benzo[a]pyrene,* Agency for Toxic Substances and Disease Registry, US Department of Human and Health Services

ATSDR (1993) Polycyclic aromatic hydrocarbon toxicity. *Am. Fam. Physic., 47,* 623–628

ATSDR (1995) *Toxicological profile for polycyclic aromatic hydrocarbons,* Agency for Toxic Substances and Disease Registry, US Department of Human and Health Services

Dennis, M.J., Massey, R.C., McWeeny, D.J., Knowles, M.E. & Watson, D. (1983) Analysis of polycyclic aromatic hydrocarbons in UK total diets. *Fd. Chem. Toxicol.*, *5*, 569–574

Gustavsson, P. (1989) Mortality among workers at a municipal waste incinerator. *Am. J. Indust. Med*, *15*, 245–253

IARC (1983) *IARC monographs on the evaluation of carcinogenic risks to humans*, Vol 32, *Polynuclear aromatic compounds, Part 1, Chemical, environmental and experimental data*, Lyon, France, International Agency for Research on Cancer

IARC (1984) *IARC monographs on the evaluation of carcinogenic risks to humans*, Vol 34, *Polynuclear aromatic compounds, Part 3, Industrial exposures in aluminium production, coal gasification, coke production, and iron and steel founding*, Lyon, France, International Agency for Research on Cancer

IARC (1987) *IARC monographs on the evaluation of the carcinogenic risks to humans*, Supplement 7, *Overall evaluations of carcinogenicity: an updating of IARC monographs Volumes 1–42*, Lyon, France, International Agency for Research on Cancer

IARC (1994) *DNA adducts: identification and biological significance*, Hemminki K., Dipple A., Shuker D.E.G., Kadlubar F.F., Segerbäck D. & Bartsch H., eds, IARC Scientific Publications, No. 125, Lyon, France, International Agency for Research on Cancer.

Mumford, J., Li, X., Chuang, J., Lewtas, J., Hu, F., Lu, S., Shank, T. & Gallagher, J. (1993) Mutagens, polycyclic aromatic hydrocarbon metabolites, DNA adducts and lung cancer from indoor exposure to coal emissions (Meeting abstract). *Proc. Annu. Meet. Am. Assoc. Cancer Res.*, *34*, A905

Nisbet, Z.C.T. & LaGoy, P.K. (1992) Toxic equivalency factors (TEFs) for polycyclic aromatic hydrocarbon (PAHs). *Regulat. Toxicol. Pharmacol.*, *16*, 290–300

Seto, H., Ohkubo, T., Kanoh, T., Koike, M., Nakamura, K. & Kawahara, Y. (1993) Determination of polycyclic aromatic hydrocarbons in the lung. *Arch. Environ. Contam. Toxicol.*, *24*, 498–503

Stavric, B. & Klassen, R. (1994) Dietary effects on the uptake of benzo[*a*]pyrene. *Fd. Chem. Toxicol. 32*, 727–734

Ström, J., Alfredsson, L., Gustavsson, P. and Malmfors, T. (1993) Polycyclic aromatic hydrocarbons and cardiovascular disease — a review of the epidemiologic and toxicologic evidence for an etiologic relationship. *J. Occup Med Toxicol*, *2*, 311–335

WHO (1987) *Air quality guidelines for Europe* (European Series No. 23), Copenhagen, Denmark, World Health Organization

2.9 POLYCHLORINATED BIPHENYLS

2.9.1 INTRODUCTION

Polychlorinated biphenyls (PCBs) are a class of synthetic organic chemicals with a characteristic structure. Under trade names such as Aroclor and Fenclor, over one million tonnes of PCBs were produced for commercial use in capacitors and transformers, as hydraulic fluids and as plasticisers in paint (WHO, 1993). During the 1950s this large-scale manufacture led to environmental contamination by PCBs. Although the commercial use of PCBs has since been phased out, incineration processes continue to produce PCBs, probably through the dimerisation of chlorophenols (Kimbrough, 1995).

Of the 209 different PCB congeners only 36 are of significant environmental concern (Kimbrough, 1995). PCBs are highly lipophilic and stable, which accounts for their ability to bioaccumulate both in the environment and in humans. The stability, metabolism, and elimination of PCBs in humans depends on the number and position of the chlorine atoms on the benzene rings. The half-lives of individual PCBs generally increase with increasing chlorination, from 6 months–3 years for the less chlorinated PCBs to 16 months–30 years for highly chlorinated congeners (Yakushiji *et al.*, 1984; Lauwerys & Hoet, 1993).

Glucuronidation is an important route of PCB metabolism, as glucuronyl conjugates are eliminated more readily from the body than the parent compound. People with deficient or underdeveloped glucuronyl transferase systems, such as fetuses, newborn babies and individuals suffering from Gilbert's syndrome or Crigler and Najjar syndrome, are therefore potentially more vulnerable to the toxic effects of PCBs. Breastfed children may be at additional risk because of a steroid released in milk which inhibits glucuronyl transferase activity (ATSDR, 1995).

Food is the primary source of human exposure to PCBs although natural gas, which contains PCBs, can be a source of indoor exposure. Meat, fish and dairy products are the main foods containing PCBs. The estimated range of exposures for the general population world-wide is 0.53–14 µg/day, which for a 70 kg person equates to <0.01–0.2 µg/kg bw/day (Duarte-Davidson & Jones, 1994). The UK estimates fall towards the lower end of this range (see below), although it should be noted that estimates of average dietary intake of PCBs vary between different countries due to differences in diet, geographical location and the methods of analysis and sampling. In the workplace, inhalation and dermal routes are of particular importance.

Background levels of PCBs have been reported for the UK in the air and diet. The total average air concentration of 29 PCB congeners measured at four sites in 1993 was 0.0007 µg/m^3 (see Table 2.12.1). Assuming that 20 m^3 of air is breathed by an individual per day and that 100% (worst case) of the inhaled PCB dose is absorbed, this equates to an intake of approximately 0.014 µg/person/day. Between 1982 and 1992 the total average intake of 53 PCB congeners in the diet was estimated to have fallen from 1 µg/person/day to 0.34 µg/person/day (see Table 2.12.1).

The ability of PCBs, which are highly lipophilic, to cross the placenta and to accumulate in mammary tissue, from where they are excreted in breast milk, may lead to high exposures in fetuses and neonates. The daily intake of breastfed babies (3–11 µg/kg bw/day) is far greater than adult daily exposures (WHO, 1993). Possible developmental effects of PCBs on young children may make these higher exposures toxicologically significant (WHO, 1993; Kimbrough, 1995).

There is a large body of epidemiological data on the outcome of human exposure to PCBs and Table 2.9.1 summarises some of the reported effects. It should be noted that exposure estimates provided in the Table have been taken from studies where exposure data were available.

2.9.2 NON-CARCINOGENIC EFFECTS

A number of toxic endpoints are firmly associated with exposure of animals to PCBs but similar findings have not been confirmed in humans (ATSDR, 1989).

Table 2.9.1 Human exposure to PCBs

Effect	Nature of exposure	Exposure estimate	Results	Comments
Occupational studies				
Respiratory effects	Aroclor-exposed workers for greater than 5 years	0.007–0.011 mg/m^3 (mean air concentrations)	Respiratory tract irritation (48%); cough (14%); tightness of chest (10%)	Inconclusive association due to limitations in the study
Cardiovascular effects	194 capacitor workers exposed to Aroclor 1254, 1242 and 1016 for an average of 17 years	0.69 mg/m^3 (geometric mean taken from one area of the plant)	No reported abnormalities Measurements of systolic and diastolic blood pressure and ECG traces	
Gastrointestinal effects	Workers exposed to PCBs, possibly due to ingestion of particles (duration not stated)	0.00001–0.012 mg/m^3	Statistically significant.General loss of appetite in exposed workers (20%) as compared with control group (4%)	
	40 male and 40 female workers exposed to Pyralene and Apirolio over an average of 12 years	Concentrations in the range 0.048–0.275 mg/m^3	Epigastric distress and intolerance to fatty foods in 50% of workers with hepatic effects	
Haematological effects	Capacitor plant workers exposed to Aroclors 1254, 1242 and 1016 for an average of 17 years	0.69 mg/m^3 (geometric mean taken from one area of the plant)	Modified populations of WBCs	Limited due to exposure characterisation

(continued…)

Table 2.9.1 Human exposure to PCBs (continued)

Effect	Nature of exposure	Exposure estimate	Results	Comments
Hepatic effects	Electrical equipment manufacturers and repair workers exposed for an average of 12 years	0.048–0.275 mg/m^3	18% of workers exposed developed hepatomegaly and/or showed elevation of serum enzymes	Possibility of confounding factors
Endocrine effects	55 transformer maintenance workers exposed to Aroclor 1260 for an average of 4 years	0.00001–0.012 mg/m^3	Decrease in mean levels of thyroxine; increase in mean urinary excretion of 17–hydroxycorticosteroids	A significant correlation was noted
Dermal effects	Workers exposed for an average duration of 14.3 months	0.1 mg/m^3	Mild to moderate chloracne observed in 7 out of 14 workers	A good link, but CDFs are possible confounders
Neurological effects	Workers exposed to various Aroclors for 5 years or longer	Mean area concentration 0.007–11 mg/m^3	48% of workers exposed had symptoms of headache, dizziness, depression, fatigue and restlessness	
Reproductive effects	Male transformer repair workers exposed to Aroclor 1260	0.00001–0.012 mg/m^3	No fertility abnormalities detected. Tests included testicular examination and sperm counts	Inconclusive, and possibilities of confounders

(continued…)

Table 2.9.1 Human exposure to PCBs (continued)

Effect	Nature of exposure	Exposure estimate	Results	Comments
Cancer	Workers at two sites who were exposed to PCBs for at least 3 months	Historical exposure data not available but personal TWA in 1977 were 0.024–0.393 mg/m^3 and 0.170–1.26 mg/m^3	4 cases of rectal cancer *vs* 1.19 expected. 7 years after initial investigation, 5 cases of liver, gall bladder,and/or biliary tract cancer *vs* 1.9 expected	Limited by experimental design and possible confounders
General population study				
Developmental effects*	The offspring of mothers exposed to PCB-contaminated fish in Michigan	Cord serum levels: Control: 4 µg/l Fish-eating mothers: 9 µg/l	A dose-dependent link between PCB exposure and visual memory recognition	Evidence of impaired development, but limitations do not allow a firm conclusion to be drawn

Data from ATSDR (1995)

* Data from Brouwer *et al.* (1995), Kimbrough (1995)

CDFs, chlorinated dibenzofurans; ECG, electrocardiogram; WBCs, white blood cells

Comparison of human and animal data has led reviewers to conclude that humans are not as sensitive to PCBs as are other primates and rodents. This variation in sensitivity is likely to be due to interspecies differences in the toxicokinetics and toxicodynamics of PCBs. The following paragraphs give an overview of current thinking on specific endpoints.

Much of the human data comes from studies of populations affected by accidental exposures. The Yusho and Yu-Cheng incidents followed the consumption of contaminated rice oil; in Michigan, people were exposed to PCBs in fish caught from Lake Michigan. It is not clear whether *in utero* exposure or breastfeeding was responsible for some of the adverse effects encountered, as effects were also seen in bottle-fed children. It was apparent from the incidents that the cumulative dose of PCBs is more important than the daily dose, unless the exposure is a very large single dose.

LAKE MICHIGAN FISH EXPOSURE

Data on possible toxicity at low levels of exposure come from a series of studies of a group of pregnant women who ate moderate amounts of fish from Lake Michigan. The lake was known to be contaminated with PCBs. The exposed group was compared with a control group of women who did not eat local fish before or during pregnancy. For the exposed group the mean levels of PCBs were 4.7µg PCB/l (95% CI = 1.1–14.3) in maternal serum, 2.0 µg PCB/l (95% CI = 0.1–7.2) in cord serum and 19.3 µg PCB/l (95% CI = 5.4–63.1) in milk. A dose-dependent association between exposure to PCBs and adverse developmental effects in children was not correlated with exposure to other contaminants (DDE, PBB and lead). Although a number of confounders were controlled for in this investigation, other possible limiting factors, such as maternal intelligence, nutritional factors and exposure to methylmercury, were not studied. Also, the study did not fully describe non-participants and drop-outs (Nord, 1992).

THE YUSHO AND YU-CHENG ACCIDENTS

In June 1968 people with chloracne were admitted to a local hospital in Japan. It subsequently became clear that these patients had eaten rice oil contaminated with 375 mg/kg of PCBs, 11.6 mg/kg of polychlorinated dibenzofurans (PCDFs) and 0.8 mg/kg of polychlorinated dibenzodioxins (PCDDs). The estimated average daily intake was 157 µg/kg bw/day of PCBs and 0.9 µg/kg bw/day of PCDFs. By 1982 2000 Yusho (rice oil disease) patients had been identified.

A similar accident in Yu-Cheng, Taiwan, in 1979 again affected around 2000 individuals. This time the concentrations of contaminants in the oil were 53–99 mg PCBs/kg and 0.18–0.40 mg PCDFs/kg. Thus exposure to PCBs in these two incidents was relatively high (in the order of 70–100 µg/kg/day PCBs).

The main toxic effect of these two incidents was chloracne. Some people also suffered from a chronic bronchitis-like syndrome, and other effects included:

- ❒ hyperpigmentation;
- ❒ swelling and secretion from the meibomian glands of the eyes;
- ❒ increased liver serum enzymes;
- ❒ increased susceptibility to infections, and decreased cellular immunity;
- ❒ increased rates of miscarriage; and
- ❒ decreased birth weights and hyperpigmentation of surviving babies.

Between 1985 and 1992 a follow-up study examined the children who were newborn at the time of the Yu-Cheng incident and those subsequently born to exposed mothers. They were compared with control populations as well as people exposed in the Michigan incident. The results are indicated below.

- ❒ Dermatological ailments persisted, but no acne or hyperpigmentation was found. No dermatological effects were seen in the Michigan cohort.
- ❒ The Bayley scale of infant development was administered to children 6 months to 2.5 years old. Yu-Cheng children scored lower in both mental (100 *vs* 106, $p<0.05$) and psychomotor tests (101 *vs* 108, $p<0.05$) compared with controls. Impaired cognitive function was seen in the Michigan cohort.
- ❒ The Yu-Cheng children had an increased history of frequent bronchitis, upper respiratory infections and ear infections, a finding which was not reported in the Michigan cohort.
- ❒ Boys aged 11–14 whose mothers were exposed to PCBs had shorter penises than their controls. It is possible that this was due to hormone dysfunction.

Guo and co-workers (Guo *et al.*, 1995) have proposed two possible reasons to explain the more pronounced toxic effects observed in the Yu-Cheng incident compared with the Michigan exposure.

- The total exposure to PCBs and related compounds was higher in the Yu-Cheng incident.

- The Yu-Cheng incident, unlike the Michigan exposure, involved polychlorinated dibenzofurans, terphenyls and quaterphenyls as well as PCBs. It is difficult to separate the effects of these compounds, but because PCDFs are more toxic than PCBs it is likely that they played a part in many of the toxicities noted at Yu-Cheng (Nord, 1992).

OTHER STUDIES

Evidence linking cardiovascular, endocrine, haematological, musculoskeletal, immunological and neurological effects in humans with occupational exposure to PCBs has been inconclusive (see Table 2.9.1; ATSDR, 1995). This does not necessarily mean that PCBs have no effect on these systems, but rather that the observations were based on studies which were limited due to the small number of subjects or the way in which they were conducted. Some of these effects were observed in the Yusho and Yu-Cheng incidents, although they were not necessarily directly linked with PCB exposure.

A number of studies seem to show that inhaling PCBs causes respiratory effects such as impaired lung function, respiratory irritation and tightness of the chest. It has, however, proved difficult to attribute these symptoms firmly to PCBs because of limitations in the studies and exposure to possible confounding agents (ATSDR, 1995).

Co-planar PCBs are anti-oestrogenic (IEH, 1995) and it is therefore plausible that they may have adverse effects on reproductive function. In a study by Bush *et al.* (1986), an inverse correlation between the motility of sperm and the concentration of three PCB congeners was found when the sperm counts were less than 30 million cells/ml. However, these findings must be treated as preliminary due to the lack of information on possible confounders and the multiple statistical analysis used.

A number of studies have raised the question of whether PCBs cause developmental defects in the offspring of highly-exposed mothers. Two studies cited by the ATSDR (1995) and Kimbrough (1995) suggested that there might be such a link; in these cases the mothers had been exposed to PCBs from contaminated fish in Michigan and North Carolina. There were, however, limitations in both studies. Lower scores in developmental and cognitive tests were also observed in Yu-Cheng children.

Gastrointestinal effects have been known to occur in workers exposed to PCBs; symptoms include loss of appetite, epigastric distress and intolerance to fatty foods. These symptoms may occur as a result of the irritant action of PCBs on the stomach lining (ATSDR, 1995).

PCBs are used as experimental tools to induce microsomal enzymes in animals. If the same effect occurs in humans its toxicological significance is not clear, although it may facilitate the metabolism and ultimate elimination of PCBs. This induction has not been confirmed in people exposed to PCBs because a number of other factors also able to induce enzymes have not been controlled in the studies reported to date (ATSDR, 1995; Nord, 1992).

Dermal lesions were a feature of the Yusho and Yu-Cheng incidents. The symptoms included chloracne and hyperpigmentation. Because of the possibility of confounding by PCDFs a firm association between PCBs and skin pathology could not be confirmed (ATSDR, 1995; Nord, 1992).

Eye irritation, conjunctivitis and swollen eyelids can occur when individuals are exposed to PCBs, but it is unclear whether this is due to systemic effects or local contact (ATSDR, 1995).

2.9.3 CARCINOGENIC EFFECTS

In reviewing the possible carcinogenic effects of PCBs, both the ATSDR (1995) and Kimbrough (1995) concluded that the evidence linking PCBs with cancer in humans is inconclusive for both people exposed occupationally and the general population. Limitations of the studies as well as inconsistent results may account for this.

The role that PCBs may play in the aetiology of breast cancer is unclear. A study conducted by Falck *et al.* (1992) showed an association between PCB exposure and breast cancer, although an earlier study by Unger *et al.* (1984) did not.

The EPA has classified PCBs as Group 2B carcinogens (ATSDR, 1995) — probable human carcinogens for which there is inadequate evidence of carcinogenicity in humans but sufficient evidence in animals. IARC (1987) has classified PCBs as Group 2A carcinogens (possibly carcinogenic to humans) on a similar basis. A plausible upper-limit estimate by the EPA suggests that a lifetime exposure to 1 µg PCB/kg/day would result in an additional 77 cases of cancer in a population of 10 000 (ATSDR, 1989).

2.9.4 EXPOSURE LIMITS AND GUIDELINES

A Nordic committee assessing the risks of PCBs said that it could not recommend a TDI for either total PCBs or individual congeners because of the lack of data. Breastfeeding was endorsed on the basis that the benefits outweigh the possible risk, but the committee was unable to determine the size of the safety margin for breastfeeding — if indeed one exists. The expert group recommended measures to reduce, where possible, environmental contamination by PCBs (Nord, 1992). The Health and Safety Commission's Advisory Committee on Toxic Substances has recommended that a maximum exposure limit be set for PCBs (HSE, 1996).

Table 2.9.2 shows exposure limits and guidelines set by UK and US government agencies for PCBs.

Table 2.9.2 Exposure limits and guidelines for PCBs

Agency	Form of PCBs	Exposure limit/guideline	Reference
HSE	42% chlorinated biphenyls	1 mg/m^3 (OES; 8-hr TWA RP)	HSE, 1992
	54% chlorinated biphenyls	0.5 mg/m^3 (OES; 8-hr TWA RP)	"
EPA	Aroclor 1254	0.02 µg/kg bw/day (RfD)	ATSDR, 1995
	Aroclor 1016	0.07 µg/kg bw/day (RfD)	"
OSHA	42% chlorinated biphenyls	1 mg/m^3 (PEL; 8-hr TWA RP)	"
	54% chlorinated biphenyls	0.5 mg/m^3 (PEL; 8-hr TWA RP)	"

PEL, permissible exposure limit; RP, reference period

2.9.5 SUMMARY

Information on the human effects of PCBs has come mainly from populations exposed as a result of major dietary contamination. Few adverse effects have been definitely associated with low-level long-term exposure. Subtle developmental and reproductive effects may occur in children exposed *in utero* or through breastfeeding. There is inadequate evidence for human carcinogenicity of PCBs. The current concern over human exposure to these compounds is due to their undoubted toxicity in animals and their persistence in human tissues.

2.9.6 REFERENCES

ATSDR (1989) *Public health statement on PCBs*, Agency for Toxic Substances and Disease Registry, US Department of Health and Human Sciences

ATSDR (1995) *Toxicological profile on polychlorinated biphenyls*, Agency for Toxic Substances and Disease Registry, US Department of Health and Human Sciences

Brouwer, A., Alhborg, U.G., Van der Berg, M., Birnbaum, L.S., Boersma, E.R., Bosveld, B., Denison, M.S., Gray, L.E., Hagmar, L., Holene, E., Huisman, M., Jacobson, S.W., Jacobson, J.L., Koopman-Essebom, C., Koppe, J.G., Kulig, B.M., Morse, D.C., Muckle, G., Peterson, R.E., Sauer, P.J.J., Seegal, R.F., Smits-Van Prooije, A.E., Touwen, B.C.L., Weisglas-Kuperus, N. & Winneke, G. (1995) Functional aspects of developmental toxicity of polyhalogenated aromatic hydrocarbons in experimental animals and human infants. *Eur. J. Pharmacol. Environ. Toxicol. Pharmacol., 293*, 1–40

Bush, B., Bennett, A.H. and Snow, J.T. (1986) Polychlorobiphenyl congeners *p,p´´*-DDE and sperm function in humans. *Arch. Environ. Contam. Toxicol., 15*, 333–341

Duarte-Davidson, R. & Jones, K.C. (1994) Polychlorinated biphenyls (PCBs) in the UK population: estimated intake, exposure and body burden. *Sci. Tot Environ., 151*, 131–152

Falck, F. Jr, Ricci, A. Jr, Wolff, M.S., Godbold, J. & Deckers, P. (1992) Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch. Environ. Health, 47*, 143–146

Guo, Y.L., Lambert, G.H. & Hsu, C. (1995), Growth abnormalities in the population exposed *in utero* and early postnatally to polychlorinated biphenyls and dibenzofurans. *Environ. Health Perspect., 103*, 117–122

HSE (1992) *Occupational exposure limits 1992* (Health and Safety Executive EH40/92), London, UK, HMSO

HSE (1996) *Occupational exposure limits 1996* (Health and Safety Executive EH40/96), Sudbury, UK, HSE Books

IARC (1987) *IARC monographs* on *evaluation of carcinogenic risks to humans*, Supplement 7, *Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1–42*, Lyon, France, International Agency for Research on Cancer

IEH (1995) *Environmental oestrogens: Consequences to human health and wildlife* (Assessment A1), Leicester, UK, MRC Institute for Environment and Health

Kimbrough, R.D. (1995) Polychlorinated Biphenyls (PCBs) and human health: an update. *Crit. Rev. Toxicol., 25*, 133–163

Lauwerys, R.R. & Hoet, P. (1993) *Industrial Chemical Exposure: Guidelines for Biological Monitoring* (Second Edition), London, UK, Lewis Publishers

Nord (1992) *Risk assessments of polychlorinated biphenyls* (Nord 1992: 26), Stockholm, Sweden, Institute of Environmental Medicine

Unger, M. Kiær, H., Blichert Toft, M., Olsen, J., & Clausen, J. (1984) Organochlorine compounds in human breast fat from deceased with and without breast cancer and in biopsy material from newly diagnosed patients undergoing breast surgery. *Environ. Res., 34*, 24–28

WHO (1993) *Polychlorinated biphenyls and terphenyls* (International Programme on Chemical Safety, Environmental Health Criteria, 140), Geneva, Switzerland, World Health Organization

Yakushiji, T., Watanabe, I., Kuwabara, K., Tanaka, R., Kashimoto, T., Kunita, N. & Hara, I. (1984) Rate of decrease and half-life of polychlorinated biphenyls (PCBs) in the blood of mothers and children exposed to PCBs. *Arch. Environ. Contam. Toxicol., 13*, 341–345

2.10 PARTICULATE MATTER (PM_{10})

2.10.1 INTRODUCTION

Small particles of respirable size are always present in ambient air, but there has been a change in the nature of these particles in the UK over the past three decades. Before the 1960s the main source of domestic heat was coal combustion, which was a significant contributor to particulate-based smog. Now it is particles arising from the use of diesel fuel that make up a large proportion of the particulate matter in polluted atmospheres (Seaton *et al.*, 1995).

The atmospheric formation of secondary particles by the chemical reactions of gases such as nitrogen oxides (NO_x), sulphur oxides (SO_x) and ammonia (NH_3) is another significant source of particulates. The remaining fractions are composed of:

- dust formed by the attrition of road surfaces, soil and rocks;
- fumes and dust from industrial processes;
- pollen grains, fungal spores and other biological materials; and
- dust and ash from forest fires and volcanic eruptions

(EPAQS, 1995)

Inhalation is the major route of exposure to airborne particles, and those particles that reach the deep lung are of greatest concern in terms of toxicity. The so-called PM_{10} fraction consists of those particles that pass through a size-selective orifice

with a 50% collection efficiency cut-off at 10 µm aerodynamic diameter. This fraction contains those particles most likely to reach the lung acinus (the alveoli), and is used as a surrogate measure for those particles reaching this target tissue.

Since PM_{10} particles are defined simply by their aerodynamic size, it follows that their chemical compositions differ. Some PM_{10} particles are aerosols of inorganic salts, whilst others may be carbon particles with adsorbed carcinogens such as benzo[*a*]pyrene. It appears from the epidemiological findings, however, that dose–response data for several endpoints are consistent regardless of the particles' nature. It therefore seems that size is a good predictor of toxicity, irrespective of particle chemistry.

Exposure to small particulates is now associated with both acute and chronic effects, and with exacerbation of pre-existing disease. The vast majority of the evidence linking exposure to PM_{10} particles with adverse health effects comes from studies of exposure of the general public. The number of studies relating changes in PM_{10} levels to disease endpoints is extensive, and only selected primary papers are cited here. A number of current review articles are reflected in this summary (COMEAP, 1995; EPAQS, 1995).

Estimated average daily levels of PM_{10} in the UK are in the range 20–34 µg/m^3 (COMEAP, 1995; EPAQS, 1995; see Table 2.12.1) but levels above 50 µg/m^3 are not uncommon, particularly in cities.

2.10.2 NON-CARCINOGENIC EFFECTS

Exposure to PM_{10} particles causes a number of health effects in the general population. The most consistent are acute cardiopulmonary symptoms and increased rates of mortality over a long term. These effects are more likely to predominate in susceptible populations: the old, people who smoke, and those with existing pulmonary disease or cardiovascular disorders such as heart disease and atherosclerosis (Seaton *et al.*, 1995). Such groups may be particularly vulnerable when living near significant sources of PM_{10}.

Traditionally, controlled experiments have been used to establish the links between gaseous atmospheric pollutants (such as nitrogen dioxide (NO_2), SO_2 and ozone) and their acute toxic effects. For PM_{10}, however, expert panels have had to rely on epidemiological data and to a smaller extent on animal studies.

Although the link between adverse health effects and PM_{10} exposure is now widely accepted as causal, the exact mechanisms of toxicity are not yet known.

ACUTE EFFECTS

Evidence for acute effects of exposure to PM_{10} particles comes mainly from time-series epidemiological studies. Studies have had as their endpoints, for example, increased number of hospital admissions, increased number of prescriptions and increased daily mortality ratios.

Dockery and Pope (1994) reviewed a selection of epidemiological studies of US cities covering a number of acute endpoints. They found that each daily increase of 10 µg/m^3 in PM_{10} concentration was associated with:

- increased overall mortality (1%);
- increased cardiovascular mortality (1.4%);
- increased respiratory mortality (3.4%);
- increased hospital admissions (0.8%) and emergency room visits (1%) — for asthmatics, emergency room visits were up by 3.4%;
- more hospital visits for asthma attacks (1.9%); and
- more respiratory attacks in asthmatics (3%).

The reviewers concluded that short-term increases in particle levels may, in some instances, precipitate a substantial health burden on susceptible individuals and hospitals. For example, on the basis of the findings above, an increase of 50 µg/m^3 would produce an estimated 16% increase in attacks of asthma.

Although a number of studies have shown excess daily mortality, a recent analysis by Styer *et al.* (1995) failed to corroborate the association between PM_{10} and

mortality. In this study a linear regression model of daily mortality took account of meteorological variables (such as cloud cover, wind speed and direction) and outdoor levels of PM_{10}. Two locations were studied; at one site there was no correlation whilst at the other there was evidence of a positive effect in spring and autumn, but not in summer or winter.

A number of other endpoints have been used in assessing the impact of exposure to particulate matter on human health. These include respiratory symptoms, restricted activity days and absenteeism from school (see Pope *et al.*, 1995a) for a summary of the different studies, endpoints and outcomes). The WHO has amalgamated epidemiological data on the acute health effects of PM_{10} exposure and concluded that there is a linear dose–response at the levels studied. Generally, a short-term rise of 10 μg/m^3 appears to be associated with a 1% increase in mortality (see Table 2.10.1).

Table 2.10.1 Daily average concentration of PM_{10} needed to produce particular effects

Effect	% increase in effect	Estimated rise in daily average concentration of PM_{10} needed for a given effect (μg/m^3)
Daily mortality	5%	50
	10%	100
	20%	200
Hospital admissions for respiratory conditions	5%	25
	10%	50
	20%	100
Bronchodilator use among asthmatics	5%	7
	10%	14
	20%	29
Symptom exacerbation among asthmatics	5%	10
	10%	20
	20%	40
Peak expiratory flow (mean population change)	5%	200
	10%	400
	20%	–

From WHO (1994)

In reviewing the epidemiological data, Dockery and Pope (1994) found no acute increases in mortality associated with carcinogenic, non-pulmonary and non-cardiovascular effects.

Some occupational studies have been carried out on workers exposed to high concentrations of particulate matter, but these have failed to show any overall increase in mortality (Seaton *et al.*, 1995). The authors proposed two explanations for this finding: first, that workers were exposed to inhalable rather than respirable matter (i.e. larger particles) and second, that industrial workers do not reflect the proportion of 'at risk' individuals in the general population.

CHRONIC EFFECTS

Unlike the acute effects, which are seen after one or two days of exposure, the mortality and chronic morbidity resulting from long-term exposure to PM_{10} have been difficult to assess. Factors such as lack of historical data, changes in the concentration and composition of pollutants, and the fact that people change location make long-term assessment difficult (COMEAP, 1995).

According to COMEAP (1995), the most carefully conducted long-term mortality study was carried out by Dockery and co-workers on adult residents of six US cities. The study followed a population of more than 8000 exposed to differing levels of air pollution over a 16-year period. After adjusting for sex, age, smoking habits, education level, occupation and body mass, it was found that mortality rates were associated with several pollutants, but most closely with fine particles (<2.5 μm) or sulphates. The adjusted mortality rate ratio in the most polluted city (mean fine particle concentration 29.6 $\mu g/m^3$) to that of the least polluted (mean fine particle concentration 11.0 $\mu g/m^3$) was 1.26, with the other cities having intermediate values. As far as could be determined, excess death was due to cardiopulmonary causes and lung cancer (Dockery *et al.*, 1993).

Collective analysis of the available data indicated a link between the SO_2/particle complex associated with coal burning and bronchitic (as opposed to asthmatic) effects. However, the committee also pointed out the possible limitations of these studies (COMEAP, 1995). The WHO concluded that, on the basis of studies carried out on adults in the mid-1980s, health effects were only discernible at mean concentrations of black smoke (a sampling term representing the dark stain obtained on a white filter paper through which air has been passed; WHO, 1987) and SO_2 each above 100 $\mu g/m^3$.

2.10.3 CARCINOGENIC EFFECTS

The suggestion that PM_{10} may be carcinogenic to humans arises from the observation that the incidence of lung cancer is higher in urban than in rural areas. It is also known that carcinogens such as benzo[*a*]pyrene may be adsorbed onto particles. However, the link between lung cancer and exposure to suspended particulate matter has been difficult to assess because of the confounding influence of smoking (COMEAP, 1995).

An association between PM_{10} exposure and lung cancer has been established, to a limited extent, in workers occupationally exposed to diesel exhausts (Gershick *et al.*, 1988), and more recently in a cohort study carried out in the USA (Pope *et al.*, 1995b). IARC classified diesel exhaust as a probable human carcinogen (Group 2A), on the basis of data for humans exposed occupationally at high levels (although these findings were inconsistent), and of positive results in experimental animals (IARC, 1989). In the study conducted by Pope *et al.* (1995b), the relative risk of developing cancer from exposure to fine particles (those with an aerodynamic diameter equal to or less than 2.5 µm) was only 1.03 (95% CI = 0.80–1.33); this value was obtained by comparing the most polluted and least polluted areas, where the difference in concentration was 24.5 µg/m^3.

An EPAQS committee and the Department of Health Committee on the Medical Effects of Air Pollutants (EPAQS, 1995; COMEAP, 1995) concluded that for the general population, at the levels of PM_{10} encountered in the environment, the risk of developing cancer was "exceedingly small".

2.10.4 EXPOSURE LIMITS AND GUIDELINES

A number of UK and international committees and panels have been constituted to address the problem of setting safe or permissible levels of PM_{10}. They have relied heavily on epidemiological data in making their assessments. At the levels studied, the dose–response appears to be linear for the endpoints highlighted in Table 2.10.1. However, at the higher levels of exposure (several hundred µg/m^3),

which have occurred in the former GDR and China, there appears to be a shallower gradient in terms of mortality (WHO, 1995).

The epidemiological data does not support the existence of a threshold below which it can be stated that no adverse effect occurs (Pope *et al.,* 1992; 1995a). Guidelines for environmental concentrations have therefore generally been set at levels deemed to pose a risk to the smallest possible number of people. In 1987 the WHO set a tentative value of 70 µg/m^3, based on a single study which also involved SO_2 (WHO, 1987). In 1994 this value was withdrawn on the basis that existing studies had been unable to establish a threshold. The WHO, therefore, has not set an air quality standard for Europe.

The UK EPAQS committee recently set a value of 50 µg/m^3 (equivalent to 1 mg in 24 hr) as a 24 hr average for the UK, with the express aim of ensuring a decline in both peak and annual average concentrations. In recommending this value the panel recognised that a number of judgements had had to be made based on insufficient scientific evidence. The average daily exposure estimates for the UK are currently 20–30 µg/m^3 (COMEAP, 1995; EPAQS, 1995; see Table 2.12.1), but excursions above 50 µg/m^3 are relatively common, especially in cities.

2.10.5 SUMMARY

Exposure to PM_{10} particles is associated with increased acute and chronic morbidity and mortality from a variety of causes in the general population, particularly in susceptible subgroups. These effects do not appear to have a threshold and are dose-dependent. It has been estimated that a 10 µg/m^3 increase in daily PM_{10} levels is associated with a 1% increase in daily mortality, as well as increases in various morbidity endpoints.

2.10.6 REFERENCES

COMEAP (1995) *Non-biological particles and health*, Committee on Medical Effects of Air Pollution, London, UK, HMSO

Dockery, D.W., Pope, C.A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., Ferris, B.G. & Speizer, F.E. (1993) An association between air pollution and mortality in six US cities. *New Eng. J. Med., 329,* 1753–1759

Dockery, D. & Pope, C.A. (1994) Acute respiratory effects of particulate air pollution. *Ann. Rev. Public Health, 15,* 107–132

EPAQS (1995) *Particles,* Expert Panel Air Quality Standards, London, UK, HMSO

Gershick, E., Schenker, M.B. & Munoz, A. (1988) A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. *Am. Rev. Respir. Dis., 137,* 820–825

IARC (1989) *IARC Monographs on the evaluation of carcinogenic risks to humans,* Vol 46, *Diesel and gasoline engine exhausts,* Lyon, France, International Agency for Research on Cancer

Pope, C.A., Schwartz, J. & Ransom, M.R. (1992) Daily mortality and PM_{10} pollution in Utah Valley. *Arch. Environ. Health, 47,* 211–217

Pope, C.A., Bates, D.V. & Raizenne, M.E. (1995a) Health effects of particulate air pollution: time for reassessment? *Environ. Health Perspect., 103,* 472–480

Pope, C.A., Thun, M.J., Namboodiri, M.M., Dockery, D.W., Evans, J.S., Speizer, F.E. & Heath, C.W. (1995b) Particulate air pollution as a predictor of mortality in a prospective study of US adults. *Am. J. Respir. Crit. Care Med., 151,* 669–674

Seaton, A., MacNee, K., Donaldson, K. & Godden, D. (1995) Particulate air pollution and acute health effects. *Lancet, 345,* 176–178

Styer, P., McMillan, N., Gao, F., Davis, J. & Sacks, J. (1995) Effects of outdoor airborne particulate matter on daily death counts. *Environ. Health Perspect., 103,* 480–497

WHO (1987) *Air quality guidelines for Europe* (European Series No. 23), Copenhagen, Denmark, World Health Organization

WHO (1994) *Update and revision of the air quality guidelines for Europe*. Meeting of the Working Group on "Classical" Air Pollutants, Bilthoven, the Netherlands, World Health Organization

WHO (1995) *Update and revision of the air quality guidelines for Europe*, Copenhagen, Denmark, World Health Organization

2.11 SULPHUR DIOXIDE

2.11.1 INTRODUCTION

The main source of SO_2 in the UK is the combustion of sulphur-containing fossil fuels, predominantly coal and heavy oils. For the UK in 1994, annual mean environmental levels of SO_2 in 15 cities and other areas ranged from 1–50 μg/m^3 (see Table 2.12.1).

Inhaled SO_2 dissolves easily in the layer of fluid on the nasal and upper airway linings and is completely absorbed at these sites; little reaches the gas exchange zone of the lung (MAAPE, 1992). Exposure to very high concentrations causes painful irritation of the eyes, nose, mouth and throat. It can also result in acute chemical injury to the linings of the airways, causing serious difficulty in breathing and even death. The non-carcinogenic effects of SO_2 are of primary importance, though data on carcinogenicity are also considered briefly here.

In recent years several reviews of the effects of SO_2 on human health at the levels commonly found in ambient air have been published (MAAPE, 1992; Wardlaw, 1993; EPAQS, 1995). Both epidemiological and controlled chamber studies have been undertaken.

2.11.2 NON-CARCINOGENIC EFFECTS

The sensory irritant effects of SO_2 are caused by stimulation of the nerves in the lining of the nose, throat and airways of the lung. This causes a reflex cough, irritation, and a feeling of chest tightness, and may lead to narrowing of the

airways and a blockage of mucociliary action. These last two effects are particularly likely to occur in people suffering from asthma and chronic lung disease, whose airways are often inflamed and easily irritated (EPAQS, 1995). Data from epidemiological and controlled exposure chamber studies are summarised below.

EPIDEMIOLOGICAL STUDIES

Studies carried out in the 1950s and 1960s in the UK demonstrated that when 24-hour means of both SO_2 and black smoke exceeded 500 µg/m^3 (187 ppb*) there was an increase in mortality, especially in the elderly and sick (MAAPE, 1992).

Studies of the effects of SO_2 on morbidity in groups of patients with chronic chest disease have demonstrated clear adverse effects when 24-hour means of SO_2 and black smoke exceeded 500 µg/m^3 and 250 µg/m^3 (93.5 ppb) respectively. More recently, air pollution episodes during which concentrations of SO_2 and fine particles each exceeded 200 µg/m^3 (70 ppb) have been linked to small changes of lung function in children (MAAPE, 1992).

A recent study by Xu *et al.* (1994) investigated the relationship between SO_2, particulates and health in areas of Beijing, China. The levels of the two pollutants were reported to be high (mean SO_2 level 102 µg/m^3 (38 ppb); mean total suspended particulate (TSP) level 375 µg/m^3 (140 ppb)). A highly significant association between increases in the levels of SO_2 and daily mortality was found.

The risk of mortality from all causes was estimated to increase by 11% (95% CI = 5–16%) with each doubling of SO_2 concentration. When mortality was analysed separately by cause, the association with a doubling in SO_2 was significant for chronic obstructive pulmonary disease (29%), pulmonary heart disease (19%) and cardiovascular disease (11%), and marginally significant for other non-malignant causes (8%). In season-specific analyses, both SO_2 and TSP were found to be significant predictors of total daily mortality in summer. In winter, only increased SO_2 was associated with increased mortality.

* 1 ppb (parts per billion) is one part in 10^9 by volume. It is equivalent to 2.67 µg/m^3 at 20˚C and 1013 millibars, or to 2.86 µg/m^3 at 0˚C and 1013 millibars. The former conversion factor is used throughout this document although the latter is used in MAAPE (1992).

Wichmann & Heinrich (1995) described a retrospective study of the effects of high levels of SO_2 and particulates on daily mortality in Eufurt, East Germany, between 1980 and 1989. Dose–response relationships were found, but the increase in mortality due to an increase in SO_2 concentration appeared to be greater in autumn than in winter. The researchers explained this as a 'harvesting effect': higher mortality in the autumn reduced the pool of susceptible individuals who might die during the following winter.

A review by the WHO (1995) refers to early studies of the prevalence of respiratory symptoms and lung function in localities with contrasting airborne pollution levels, largely in the form of black smoke from the burning of coal. The LOAEL for SO_2 was judged to be an annual average of 100 µg/m^3 (35 ppb). More recent studies, some of which relate to industrial sources of SO_2, have shown adverse effects at lower levels.

A major difficulty in interpreting long-term studies and comparing modern with historical data is that the types as well as the levels of air pollution have changed over the years. Cohort studies of areas with contrasting pollution levels generally show that mortality is more closely associated with particulate material than with SO_2.

EXPOSURE CHAMBER STUDIES

Human exposure chamber studies, where volunteers are exposed to SO_2 in controlled laboratory conditions, show a dose-related bronchoconstriction response (MAAPE, 1992; WHO, 1995). Asthmatic patients are more sensitive to SO_2 than normal subjects. In normal patients, no changes in indices of lung function have been recorded following exposure to concentrations of less than 2.6 mg/m^3 (1000 ppb). In asthmatics, however, changes in lung function have been recorded at concentrations as low as 267 µg/m^3 (100 ppb), although few subjects have shown changes that are likely to be clinically important on exposure to less than 1.07 mg/m^3 (400 ppb) of SO_2.

However, it should be borne in mind that patients with severe or highly reactive asthma are usually excluded from such studies, and these individuals could well be more sensitive. Other potentially susceptible groups, such as children and individuals with chronic obstructive pulmonary disease, are also excluded for ethical reasons. Subjects who are mouth-breathing or undergoing heavy exercise have also been shown to be more sensitive; in these cases concentrations as low as 534 µg/m^3 (200 ppb) can affect lung function (MAAPE, 1992).

Exposure chamber studies suggest that the acute effects are determined more by the concentration of SO_2 than by the duration of exposure. However, acute chamber studies cannot predict the effect of prolonged exposure at lower doses (Wardlaw, 1993).

It has been suggested that exposure to SO_2 may potentiate sensitisation to inhaled allergens in animals, and some epidemiological studies suggest that people living in polluted areas are more likely to become sensitised. Whether this effect is due to SO_2 or to other factors is unknown. However, recent studies indicate that the combination of SO_2 and NO_2 can increase the sensitivity to allergens of some patients with asthma. Devalia *et al.* (1994) found that exposure of mild asthmatics to 534 µg/m^3 (200 ppb) of SO_2 and 1.07 mg/m^3 (400 ppb) of NO_2 enhanced the airway response to inhaled allergens. D'Amato *et al.* (1994) suggested that long-term low-level SO_2 exposure might increase airway hyperreactivity by enhancing allergic sensitisation in at-risk subjects, without apparent clinical effect until acute symptoms are precipitated at a later date.

2.11.3 CARCINOGENIC EFFECTS

Studies on the carcinogenic activity of SO_2 were summarised and evaluated by IARC (1992). Most of these are concerned with occupational exposure, primarily in sulphite pulp mills and copper smelting plants. IARC (1992) considered that there was inadequate evidence to classify the carcinogenicity of SO_2 , sulphites, bisulphites or metabisulphites (Group 3). Several studies of occupational exposure to acid mists, including pickling operations in the steel industry and workers in a petrochemical plant, have demonstrated excesses of sinus cancer, laryngeal cancer and lung cancer. IARC (1992) concluded from these studies that occupational exposure to mists containing sulphuric acid is carcinogenic to humans (Group 1).

2.11.4 EXPOSURE LIMITS AND GUIDELINES

Table 2.11.1 shows exposure limits and guidelines set by UK government agencies and WHO for SO_2

Table 2.11.1 Exposure limits and guidelines for SO_2

Agency	Exposure limit/guideline	Reference
EPAQS	100 ppb (267 µg/m^3; 15-min AP)	EPAQS, 1995
HSE	5 mg/m^3 (8-hr TWA RP)	HSE, 1996
	13 mg/m^3 (15-min RP)	"
WHO	500 µg/m^3 (10-min AP)	WHO, 1987
	125 µg/m^3 (24-hr AP)	"
	50 µg/m^3 (annual average)	"

AP, averaging period; RP, reference period

2.11.5 SUMMARY

Short-term exposure to SO_2 at occupational exposure levels irritates the upper respiratory tract. It can produce bronchial constriction in sensitive subjects at both occupational and environmental exposure levels. Epidemiological studies have shown that long-term environmental exposure is associated with increased cardiorespiratory morbidity and mortality. Ambient exposure may also increase sensitisation to environmental allergens. Almost all the annual mean levels of SO_2 measured at various sites in the UK in 1994 fell below the maximum annual average of 50 µg/m^3 recommended by WHO and, in those areas where data were available, levels were generally lower than in previous years.

2.11.6 REFERENCES

D'Amato, G., Liccardi, G & Cazzola, M. (1994) Environment and development of respiratory allergy: 1. Outdoors. *Monaldi. Arch. Chest Dis., 49,* 406–411

Devalia, J.L., Rusznak, C., Herdman, M.J., Trigg, C.J., Tarraf, H. & Davies, R.J. (1994), Effects of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. *Lancet, 344,* 1668–1671

EPAQS (1995) *Sulphur dioxide*, Expert Panel on Air Quality Standards, London, UK, HMSO

HSE (1996) *Occupational exposure limits 1996* (Health and Safety Executive EH40/96), Sudbury, UK, HSE Books

IARC (1992) *IARC monograph on the evaluation of carcinogenic risks to humans*, Vol 54, *Occupational exposures to mists and vapours from strong inorganic acids; and other industrial chemicals*, Lyon, France, International Agency for Research on Cancer

MAAPE (1992) *Sulphur dioxide, acid aerosols and particulates* (Advisory Group on the Medical Aspects of Air Pollution Episodes, Second Report), London, UK, HMSO

Wardlaw, A.J. (1993) The role of air pollution in asthma. *Clin. Exper. Allergy, 23,* 81–96

WHO (1995) *Update and revision of the air quality guidelines for Europe. Meeting of the Working Group "Classical" Air Pollutants*, Bilthoven, The Netherlands

Wichmann, H.-E. & Heinrich, T. (1995) Health effects of high-level exposure to traditional pollutants in East Germany — review and ongoing research. *Environ. Health Perspect., 103 (suppl 2)*, 29–35

Xu, X., Guo, J., Dockery, D.W. & Chen, Y. (1994) Air pollution and daily mortality in residential areas of Beijing, China. *Arch. Environ. Health., 49,* 216–222

2.12 SUMMARY OF EXPOSURE AND HEALTH EFFECTS

Table 2.12.1 summarises, for each of the ten pollutants, estimates of background levels/intakes in air and in the diet, the site of accumulation (if the pollutant is accumulated) and the principal health effects associated with the pollutant.

Table 2.12.1 Summary of background levels/intakes and major health effects of key pollutants from incinerators

Pollutant	Background levels		Accumulation site	Major health effects[d]
	Air[a] [intake[b]]	Diet[c]		
Cadmium	0.0053 µg/m^3 [e] [0.11 µg/person/day]	18 µg/person/day [f]	Liver and kidney	Workplace exposures associated with effects on lungs (including an increased risk of cancer) and kidneys. Environmental exposures are unlikely to result in these effects, although a very small increase in risk of lung cancer cannot be excluded
Mercury	0.00025 µg/m^3 [g] [0.0050 µg/person/day]	2 µg/person/day [f]	Mostly in the kidney for inorganic salts; Hg vapour also deposited in the brain	Changes in kidney function and behavioural effects at low exposure levels in the workplace. The relevance of these effects to environmental exposures is uncertain
Arsenic	0.016 µg/m^3 [h] [0.32 µg/person/day]	<70 µg/person/day [f]	Does not accumulate	Inorganic arsenic is toxic to respiratory tract, skin, liver and peripheral nervous system at high exposure levels; the major health effect is cancer of the skin and lungs. Any increase in cancer risk at environmental exposure levels is likely to be small and difficult to determine
Chromium	0.0036 µg/m^3 [i] [0.072 µg/person/day]	250 µg/person/day [f]	Cr (VI) does not accumulate; Cr (III), although poorly absorbed, can accumulate in liver, spleen and bone marrow	Occupational exposure to some Cr (VI) compounds is associated with damage to the inner tissues of the nose, skin inflammation and lung cancer. Effects on the nose and skin are unlikely at environmental exposures but a small increase in lung cancer risk cannot be excluded
Nickel	0.0012 µg/m^3 [i] [0.024 µg/person/day]	170 µg/person/day [f]	Concentrated in liver and kidneys (and lungs following inhalation); in individuals without known exposure, highest levels found in bone, lung, kidney, liver and heart	Workplace exposure to inorganic nickel compounds is associated with an increased risk of cancer of the lung and nose; a small increase in risk at environmental levels is possible. Nickel can cause allergic sensitisation

(continued…)

Table 2.12.1 Summary of background levels/intakes and major health effects of key pollutants from incinerators (continued)

Pollutant	Background levels Air[a] [intake[b]]	Diet[c]	Accumulation site	Major health effects[d]
PCDD/Fs	6.8pg/m^3 [j] [140 pg/person/day]	69 pgTEQ/person/day[k]	Accumulates in adipose tissue; can be detected in breast milk	Chloracne is associated with high levels of exposure. May affect metabolism, development and reproduction at levels less than ten times average levels in the body. Dioxins may also cause cancer
PAHs	0.128 µg/m^3 [l] [2.6 µg/person/day]	3.7 µg/person/day[m]	Can accumulate in adipose tissue and breast milk	Some PAHs may cause cancer of the lung, skin and possibly bladder and gut at high levels of exposure; it is not possible to estimate cancer risk at environmental exposure levels
PCBs	0.00070 µg/m^3 [n] [0.014 µg/person/day]	0.34 µg/person/day[o]	Accumulates mainly in adipose tissue (and breast milk)	Few adverse effects definitely associated with long-term low-level exposure. Subtle developmental effects reported in children resulting from exposure in the womb or through breast feeding. Evidence for ability to cause cancer is inadequate
PM_{10}	20–34 µg/m^3 [p] [400–680 µg/person/day]	Not applicable	Does not accumulate	Increased short- and long-term health effects and mortality in the general population, particularly in susceptible subgroups such as the elderly or sick
SO_2	1–50 µg/m^3 [q] (0.4–19ppb) [20–1000 µg/person/day]	Not applicable	Does not accumulate	Short-term high-level exposure can irritate the upper airways; workplace and environmental levels can produce airway narrowing in sensitive subjects. Long-term environmental exposure is associated with increased heart and lung disease and mortality, and can increase sensitisation to allergens such as pollen

(continued…)

Table 2.12.1 Summary of background levels/intakes and major health effects of key pollutants from incinerators (continued)

[a] Background air data taken from Bertorelli & Derwent (1995)

[b] The figure in square brackets is the calculated total daily background intake per person *via* the air, based on a breathing volume of 20 m^3/day

[c] Background data on dietary levels taken from MAFF (1994; 1995; 1996); Dennis *et al.* (1993)

[d] For non-cancer endpoints, thresholds may exist but the levels at which they occur are not well established

[e] Average mean annual concentrations measured at five sites (Brent, Central London, Glasgow, Leeds and Motherwell) in 1989

[f] Estimated total upper bound intake in 1991

[g] Average mean concentration measured at nine sites during the given periods: Altrincham (1978–1989), Brent (1975–1989), Chilton (1971–1988), Flixton (1975–1989), Lambeth (1976–1982), Manchester City North (1975–1989), Manchester City South (1975–1989), Walsall (1976–1989) and Wraymires (1970–1989)

[h] Average mean concentration measured at ten sites during the given periods: Altrincham (1978–1989), Brent (1975–1989), Chilton (1971–1989), Flixton (1975–1989), Lambeth (1976–1982), Manchester City North (1975–1988), Manchester City South (1975–1989), Swansea (1972–1981), Walsall (1976–1989) and Wraymires (1970–1989)

[i] Average mean annual concentrations measured at five sites (Brent, Central London, Glasgow, Leeds and Motherwell) in 1990

[j] Average total concentrations of 17 2,3,7,8-substituted dioxin and furan congeners measured at four sites (Bowland, London, Manchester and Middlesbrough) in 1993

[k] Estimated upper bound dietary intake of dioxins as toxic equivalents (TEQ) in 1992

[l] Average total concentrations of 15 PAH compounds measured at four sites (Bowland, London, Manchester and Middlesbrough) in 1993

[m] Data from Dennis *et al.* (1983). Level represents the sum of 11 PAH compounds based on estimated consumption of various food types in total diet

[n] Average total concentrations of 29 PCB congeners measured at four sites (Bowland, London, Manchester and Middlesbrough) in 1993

[o] Estimated average total intake of 53 PCB congeners in 1992

[p] Range of annual means in 1994 in Belfast, Birmingham, Bloomsbury, Bristol, Cardiff, Edinburgh, Hull, Leeds, Leicester, Liverpool, Newcastle and Southampton

[q] Range of annual means in 1994 in Barnsley, Belfast, Birmingham, Bloomsbury, Bridge Place, Bristol, Cardiff, Edinburgh, Hull, Leicester, Liverpool, Newcastle, Southampton, Strath Vaich and Sunderland

2.12.1 REFERENCES

Bertorelli, V. & Derwent, R. (1995) *Air quality A to Z: A directory of air quality data for the United Kingdom in the 1990s,* Air Quality Division, Department of the Environment

Dennis, M.J., Massey, R.C., McWeeny, D.J. & Knowles, M.E. (1983) Analysis of polycyclic aromatic hydrocarbons in UK total diets. *Fd Chem. Toxicol., 21,* 569–574

MAFF (1994) *1991 Total diet survey* (Food Surveillance Information Sheet No. 34), London, UK, Ministry of Agriculture, Fisheries and Food

MAFF (1995) *Dioxins in food — UK dietary intakes,* (Food Surveillance Information Sheet No. 71), London, UK, Ministry of Agriculture, Fisheries and Food

MAFF (1996) *Polychlorinated biphenyls in food — UK dietary intakes,* (Food Surveillance Information Sheet No. 89), London, UK, Ministry of Agriculture, Fisheries and Food

3 Epidemiological studies of populations exposed to incinerator emissions and special risk groups

3.1 SUMMARY OF EPIDEMIOLOGICAL STUDIES

3.1.1 STUDIES OF POPULATIONS LIVING NEAR INCINERATORS INCLUDING THOSE BURNING MSW

This section concentrates on published studies of morbidity or mortality in populations living near waste incinerators, specifically municipal waste incinerators. A short section covering occupational studies of incinerator workers is also included (Section 3.1.2).

Many hundreds of publications using various risk assessment methodologies deal with the estimation of likely health effects from incinerators. Relatively few of these, reviewed here, concentrate on actual measured human health effects.

In 1988, Lloyd and co-workers published a study investigating the incidence of twinning in both cattle and human populations exposed to air pollution from two incinerators (one chemical waste, the other municipal waste) near Bonnybridge in central Scotland (Lloyd *et al.*, 1988)*.

*A previous inquiry into the effects of pollutants from the chemical waste incinerator on the health of farm animals and local people had rejected the suggestion that contamination from the incinerator was the cause. Human health effects reported in this inquiry included an excess of eye defects in babies, a rise in incidence of leukaemia and a significant excess of deaths from bronchitis.

The geographical distribution of twinning was analysed for each year between 1975 and 1983 using information on single and twin births. Areas around the incinerators were designated as being at primary or secondary risk, based on a knowledge of wind direction in the area and the resulting predicted movement of fumes from the incinerators.

For human twins, background values of twinning for the area showed rates between 3 and 13 per 1000. The highest rates (20 and 16 per 1000 respectively) were found in the two primary risk sectors during 1980–83. The mean age of mothers in the 'at risk' areas was similar to that in the total study area (twinning rates increase considerably in mothers aged over 35). In the cattle population studied, the rate of twinning increased in the late 1970s (by 2%, representing three twin births) and reached a maximum in 1983 (22%, or 31 twin births).

The authors concluded that the human twinning results were consistent with the introduction into the local environment in the late 1970s of polychlorinated hydrocarbons, some of which have oestrogenic and fertility-related properties, or other chemicals with similar actions. However, they warned that it would be premature to conclude that the incinerator was the cause of this. Indeed, there are several reasons why caution is necessary. For example, no exposure data were presented. Oestrogen levels may be elevated in women who bear twins, but it is not known whether this is a cause or a result of bearing of twins. However, there has been some suggestion that the findings could be explained by a random occurrence of marginally raised twinning rates (Jones, 1989).

In a short review of waste incineration and its implications for human health, Gatrell and Lovett (1992) reported their own study on the association between the incidence of laryngeal cancer and proximity to an incinerator burning solvents and oils at Charnock Richard, near Coppull in Lancashire. The plant had operated between 1972 and 1980, during which time there had been many public complaints relating mostly to the release of irritant gases. Data on cancer registrations were available for the period 1974–1983. From an initial descriptive mapping exercise it appeared that the distribution of most cancers was similar to that of the population as a whole. The exception was laryngeal cancer: of 58 cases during the study period, five were observed in Coppull and four were within 2 km of the plant.

A statistical model was used to test whether proximity to the incinerator had a significant influence on the distribution of laryngeal cancer. The researchers assumed that there was no link between the incinerator and lung cancer, so that

rates of lung cancer simply reflected the spatial distribution of the population, and that in the absence of the incinerator the distribution of laryngeal cancer would follow the same pattern.

On this basis they found a statistically significant association between laryngeal cancer and proximity to the incinerator. By 'moving' the location of the incinerator across a map of the area and fitting the model to the 'new' source each time, the only location linked to intensity of laryngeal cancer was the incinerator site. Stomach cancer showed a similar association.

However, the authors stated that in the absence of considerably more information it was not possible to claim a causal link between laryngeal cancer and living near an incinerator. Data that were not available included residential histories of cases, the latent period over which laryngeal cancer develops, personal details including smoking habits, alcohol consumption and other risk factors, and information on background air pollution.

In 1992 the Small Area Health Statistics Unit (SAHSU) published a study of the incidence of lung and laryngeal cancers near ten waste solvent and oil incinerators in Great Britain, including the one at Charnock Richard mentioned above (Elliott *et al.*, 1992). Postcoded cancer registration data were available for the years 1974–1984 (England and Wales) and 1975–1987 (Scotland). Lag periods of five and ten years from the start-up of each incinerator were used when analysing the cancer incidence. Standardised observed/expected (O/E) ratios were assessed within distances of 0–3 km and 3–10 km of each incinerator and then aggregated over all sites. Expected values were based on regionally-adjusted national rates, with and without socio-economic stratification (using Carstairs' index). In addition, the data were tested for trend in O/E ratios with distance.

For the period corresponding to a five-year lag, the total number of cases of cancer of the larynx was 323 in males and 67 in females (197 cases at ages less than 65 and 193 in ages greater than 65). For the ten-year lag the corresponding numbers were 60 and 10, 28 and 42. For the Charnock Richard incinerator none of the O/E ratios, either within 3 km or between 3–10 km, was significantly different from unity for either type of cancer or lag period. A similar result was found when sites were stratified socio-economically. There was also no evidence, for either cancer, that risk decreased at greater distance from the incinerator.

The authors discussed several limitations in their data and methods. These included possible biases in cancer registration at the small area level and the use of a maximum lag period of only ten years — a relatively short development period

for solid tumours. In addition, it was not possible to account for factors such as stack height, abatement equipment and prevailing wind. However, it was concluded that the study presented no evidence to suggest an excess risk of cancers of the larynx or lung in residents living near waste solvent and oil incinerators.

In a short abstract, Höglund & Haglind (1993) reported a study investigating the health effects of air pollution from a waste incinerator in Sweden. A computer simulation was used to identify polluted and non-polluted areas populated by 4131 and 5946 individuals, respectively. These cohorts were followed from 1975 to 1990 for cancer incidence using a regional cancer registry. A postal questionnaire was sent to a random sample of 500 individuals in each area. Neither mortality nor cancer incidence was higher in the polluted region compared with the non-polluted region. Similarly, symptoms of airway obstructions, allergy or bronchitis did not differ between the two areas.

Shy *et al*. (1995) reported a study which simultaneously measured air quality and respiratory function and symptoms in three populations. The first group lived near a biomedical incinerator, the second near a municipal incinerator and the third near an industrial furnace burning liquid hazardous waste. Results were compared with three matched-comparison communities. Levels of air pollutants including particulates (PM_{10} and $PM_{2.5}$) and gases (hydrochloric acid, nitric acid and SO_2) were measured in each pair of communities for a period of 35 days. Organics such as PCDD/Fs were not measured.

No difference was detected in concentrations of particulate matter among the three pairs of communities; levels of $PM_{2.5}$ measured over 35 days varied from 16–32 µg/m^3 across all communities and daily concentrations ranged from 10–80 µg/m^3. When winds came from the direction of the incinerators, however, higher levels of fine particulate zinc, lead and chloride were measured. These were assumed to be markers of incinerator emissions.

Direct measurement of these pollutants, together with estimates based on a chemical mass balance receptor model (using data on wind speed, wind direction and quantitative emissions) indicated that incinerator emissions did not have even a modest impact on the routinely monitored air pollutants. For the municipal incinerator, even when the wind was blowing directly from the incinerator towards the monitoring station, less than 2% of the total fine particulate mass could be apportioned to the incinerator.

For the health survey, 2592 households (6963 individuals) participated in a baseline descriptive survey. This included a number of questions relating to

respiratory disease including both chronic and acute (allergic-type) symptoms. For the biomedical and municipal incinerators, no consistent pattern of differences in symptom prevalence was demonstrated between the populations living near the incinerators and the controls.

For the group living near the hazardous waste incinerator the odds of having had sinus trouble, chronic cough or wheezing in the past year were significantly greater than for the control community. However, when compared with the combined data for all three control communities, none of the three incinerator communities showed any pattern of excess acute or chronic respiratory symptoms.

Lung function data (forced expiratory volume in 1 second (FEV_1) and peak expiratory flow rate (PEFR)) were obtained from 100–144 individuals in each of the six communities. In each case the sample included 32–56 subjects selected according to questionnaire evidence of asthma-like symptoms during the past year ('sensitives').

Among normal subjects, mean FEV_1 and PEFR were consistently higher in the incinerator communities. Among sensitive subjects, mean PEFR values were higher in the municipal and hazardous waste incinerator communities than in the comparison communities. Values of FEV_1 did not show a consistent difference between community pairs in the sensitive group. Nasal lavage on a sub-sample of individuals from all communities suggested that living near an incinerator made no difference to either cell counts or biochemical indices of inflammation.

Morning and evening peak flow measurements indicated no difference in average peak flow or in the diurnal change in peak flow between the incinerator and comparison communities. When compared with calculated concentrations of PM_{10} (within the range 20–80 $\mu g/m^3$) or $PM_{2.5}$, no consistent effect on peak flow or diurnal variation in either sensitive or normal subjects was shown over the 35-day monitoring period.

However, the authors concluded that several features of the study tended to bias the results towards finding no effect. These included the possibility of exposure misclassification, the fact that air quality measurements were available for only a 35-day period and the exclusion of children younger than eight years (a population sub-group potentially more susceptible to respiratory effects of emissions).

The most recent study of health effects in relation to incinerators was carried out by SAHSU and investigated the incidence of cancer near MSW incinerators in Great Britain (Elliott *et al.*, 1996). Using a postcoded database, the cancer

incidence of over 14 million people living near 72 MSW incinerators was examined for the years 1974–86 (England), 1974–84 (Wales) and 1975–87 (Scotland). The numbers of observed cases were compared with regionally-adjusted national rates, after stratification using a deprivation index. Observed/expected ratios were tested for decline in risk with distance, for distances up to 7.5 km from the incinerators.

The study was divided into two parts: the first examined 20 incinerators selected at random and the second part looked at the remaining 52. In both analyses a statistically significant ($p < 0.05$) decline in risk with distance from incinerators was demonstrated for all cancers combined and for stomach, colorectal, liver and lung cancer. In the second part of the study the excess number of cancers within 1 km of an incinerator ranged from 37% for liver cancer (0.95 excess cases/10^5/year) to 5% for colorectal cancer.

However, the authors made it clear that a likely explanation of the significant findings for all cancers, stomach and lung cancer was residual confounding (socio-economic factors), and this also at least partially explained the excess risk of liver cancer. Examination of cancer registration details and death certificates indicated that there was also a substantial level of misdiagnosis of primary liver cancer. Further investigation of these cases was recommended to determine whether the increase in liver cancer cases was real or not. Although exposure data were not available, the authors added that this study included old incinerators — going back to the turn of the century — which were likely to have led to very different exposures compared with those of well-maintained modern plants.

3.1.2 OCCUPATIONAL STUDIES OF INCINERATOR WORKERS

Bresnitz *et al.* (1992) evaluated medical and exposure data for an actively employed cohort of incinerator workers in Philadelphia. The incinerator was built in 1959 with two mass burning furnaces, each of which burned 375 tons/day of waste. Male workers (n = 86) were divided into potential high- and low-exposure groups based on work site analysis by an industrial hygienist. Those in the high-exposure category had worked for at least seven months in high-exposure jobs, with a median of 15.9 years of high exposure. The study included a questionnaire (for job histories and tobacco and alcohol use), medical histories, blood and urine analyses, and physical examinations which included chest radiographs and

measurement of FEV_1, forced vital capacity (FVC), FEV_1/FVC%, and forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75\%}$).

A greater number of workers in the high-exposure group consumed alcohol on a regular basis (78.9% compared with 32.4% in the low-exposure group). The blood test results and the prevalence of haematuria were similar in the two exposure groups, and there were no clinically significant differences between the two groups. Although two parameters (creatinine and haematocrit) showed statistically significant differences between the groups, the mean differences were clinically trivial.

Blood and urine analysis for mercury, lead, arsenic and cadmium demonstrated no significant differences between the two groups, and fewer than 2% of the 471 individual blood and urine tests showed levels above the expected range for the unexposed population. The pattern of pulmonary function was similar in both groups, except that spirometric changes suggestive of small airway obstruction (SAO) in the high-exposure group were almost twice as common as in the low-exposure group. When adjusted for smoking status, the odds ratio for SAO in the high *versus* low-exposure groups was 1.19 (95% CI = 0.45 to 3.16). Among never-smokers the same analysis produced an odds ratio of 1.85 (95% CI = 0.27 to 13.1).

X-ray analysis showed that five workers, all in the low-exposure group, had changes suggestive of pleural plaques or thickening. Three of these workers were also in a group of eight individuals (five in the high-exposure and three in the low-exposure groups) having pulmonary interstitial opacifications. All eight were either current or ex-smokers or obese.

No significant difference in numbers of workers with symptoms was noted between the two groups, although hypertension was diagnosed in 34% of all the workers and in 57.5% of those aged 45–64, a level higher than that for the same age range in the US population as a whole. This was tentatively related to greater alcohol consumption in this group and/or excessive noise levels. Although the analysis was limited to current workers, the authors considered the likelihood of individual exposure misclassification to be minimal.

Gustavsson (1989) investigated mortality in a group of 174 male workers employed for at least one year between 1920 and 1985 at a municipal waste incinerator near Stockholm in Sweden. Before 1955 both household and industrial wastes were incinerated at the plant, but after this date only household waste was

incinerated until the plant closed in 1986. The workers had been employed for a mean of 18.7 years and a range of 1–52 years.

Of the 174 workers, 91 were alive at the end of the study in 1985. Causes of death for those who had died since 1951 were obtained from death statistics. Standardised mortality ratios (SMRs) were computed as O/E numbers of deaths x100. Two sets of reference values were calculated, based on national and local mortality rates respectively. Total mortality was slightly above national rates (SMR for all causes 113; 95% CI = 90–140); when local rates were used, there was no difference (SMR for all causes 99; 95% CI = 79–122). Mortality from lung cancer was higher than both national (SMR 355; 95% CI = 162–675) and local rates (SMR 197; 95% CI = 90–374), although the latter was not statistically significant.

There was also a tendency toward increased mortality from ischaemic heart disease and liver cirrhosis. When analysed by time of follow-up (1–19, 20–39 and 40+ years from first employment), a high excess risk for ischaemic heart disease was found in workers with 40 years or more since first employment. For lung cancer, an excess risk was shown for all three periods of follow-up, but the small number of cases precluded an analysis for trend. Using numbers of years employed as a measure of exposure, the excess risk for ischaemic heart disease depended entirely on those with more than 30 years of employment; for those with less than 30 years of employment, the SMRs were not significantly elevated.

Although compatible with an occupational origin, the small number of lung cancer cases precluded any definite conclusions from being made regarding the cause of the excess risk. The data supported the hypothesis that the excess of ischaemic heart disease was of occupational origin. The author considered neither the excesses of lung cancer nor those of ischaemic heart disease to be due to smoking. Emissions of PAHs from the study incinerator were said to have been higher than those from more modern incinerators because of poor combustion control, but the author was not able to attribute the excess cancers to any particular chemical exposure.

Epidemiological studies in incinerator workers and populations living near incinerators have not demonstrated a consistent excess incidence of any specific disease. However, the ability of these studies to detect adverse effects has been limited by various factors including their relatively small sizes, difficulties in accounting for possible confounding exposures (e.g. smoking and socio-economic factors), and healthy worker effects (the bias that occurs when comparing mortality and morbidity of people who are fit enough to be in employment with those of the general population).

For people living near incinerators, another problem has been the use of distance of residence from an incinerator as an index of exposure. In these studies there is a general lack of actual exposure data both *via* the air and through other routes — and the latter, in particular, may not relate simply to distance from an incinerator. There is a need for more information on how exposure relates to distance from an incinerator.

3.1.3 REFERENCES

Bresnitz, E.A., Roseman, J., Becker, D. & Gracely, E. (1992) Morbidity among municipal waste incinerator workers. *Am. J. Ind. Med.*, *22*, 363–378

Elliott, P., Hills, M., Beresford, J., Kleinschmidt, I., Jolley, D., Pattenden, S., Rodrigues, L., Westlake, A. & Rose, G. (1992) Incidence of cancers of the larynx and lung near incinerators of waste solvents and oils in Great Britain. *Lancet*, *339*, 854–858

Elliott, P., Shaddick, G., Kleinschmidt, I., Jolley, D., Walls, P., Beresford, J. & Grundy, C. (1996) Cancer incidence near municipal solid waste incinerators in Great Britain. *Brit. J. Cancer*, *73*, 702–710

Gatrell, A.C. & Lovett, A.A. (1992) *Burning questions: incineration of wastes and implications for human health*, (Research Report No 8), North West Regional research Laboratory, Lancaster University

Gustavsson, P. (1989) Mortality among workers at a municipal waste incinerator. *Am. J. Ind. Med.*, 15, 245–253

Höglund, D. & Haglind, P. (1993) Health effects of air pollution from waste incineration, In: *Proceedings of the 5th International Conference of the International Society for Environmental Epidemiology*, August 1993, Stockholm, Sweden, p 80

Jones, P.W. (1989) Twinning in human populations and in cattle exposed to air pollution from incinerators. *Brit. J. Ind. Med.*, *46*, 215–216

Lloyd, O.L., Lloyd, M.M., Williams, F.L.R. & Lawson, A. (1988) Twinning in human populations and in cattle exposed to air pollution from incinerators. *Brit. J. Ind. Med.*, *45*, 556–560

Shy, C.M., Degnan, D., Fox, D.L., Mukerjee, S., Hazucha, M.J., Boehlecke, B.A., Rothenbacher, D., Briggs, P.M., Devlin, R.B., Wallace, D.D., Stevens, R.K. & Bromberg, P.A. (1995) Do waste incinerators induce adverse respiratory effects? An air quality and epidemiological study of six communities. *Environ. Health Perspect.*, *103*, 714–724

3.2 SUSCEPTIBLE OR 'AT RISK' GROUPS

Depending upon the degree of exposure, and variations in individual physiology and pathology leading to different inherent susceptibilities, certain groups of individuals within a population may be at greater risk than others from pollutants emitted by incinerators. Examples include children, the elderly, individuals with respiratory or other diseases, pregnant women and smokers. Each of these groups is considered below in more detail.

CHILDREN

Children are potentially more exposed than adults to pollutants because they breathe more rapidly, they are more likely to breathe using their mouths (leading to increased exposure to particulate and gaseous pollutants), they are more active than adults and generally spend more time outdoors.

The effects of exposure may also be more severe. Children have narrower airways than adults, relatively immature detoxification mechanisms, a high incidence of respiratory tract infections, a different prevalence of atopic sensitivity and different patterns of reactivity. Compared with adults they need proportionately more vitamins yet may follow idiosyncratic diets, so dietary deficiencies of vitamins are more common. In addition, the effects of pollutants on children's lung growth and development may lead to a greater risk from long-term health effects.

PEOPLE OVER 65

People in this sub-group of the population tend to be more susceptible because normal physiological lung function reduces with age, they have diets that are often deficient in protective antioxidant vitamins, and they suffer more chronic cardiovascular and respiratory disorders. However, as a result of spending less time exercising outdoors, they may have a lower exposure to outdoor pollution.

PEOPLE WITH RESPIRATORY DISEASES

An increased susceptibility in this sub-group, which includes asthmatics, may be due to increased bronchial responsiveness, reduced baseline lung function and a greater likelihood of interaction between pollutants and other triggers of bronchial response. People in this group tend to be older, with the other possible risk factors associated with being elderly, and acute respiratory infection may enhance bronchial reactivity. People in this group may have increased mouth breathing, which will tend to increase their exposure, but will also have reduced levels of activity and will spend more time indoors, which will tend to decrease their exposure.

PEOPLE WITH CARDIOVASCULAR DISEASE

People with ischaemic heart disease and peripheral vascular disease may be more susceptible to the effects of pollutants because they have poor oxygen delivery to the heart muscle and other tissues. This is brought about by increases in carboxyhaemoglobin (COHb) concentration, and can cause fatal cardiac dysrhythmias.

FETUSES AND NEONATES

The fetal and neonatal periods are times of intense growth and development for many systems of the body. Exposures to chemicals during this period, particularly in the blood *via* the placenta or through breastfeeding, could result in detrimental effects which may manifest themselves either immediately or later in life.

SMOKERS

Smokers may have respiratory abnormalities such as impaired particle clearance mechanisms, small airway obstruction, increased prevalence of chronic bronchitis and emphysema, and detoxification mechanisms that are overwhelmed by smoke. The high concentrations of pollutants such as carbon monoxide and NO_x in tobacco smoke may increase COHb and have interactive consequences with ambient exposure (or alternatively may overwhelm any effects of ambient exposure). Smoking increases the chance of developing bronchial hyperresponsiveness and atopy.

4 Discussion and recommendations

4.1 GENERAL CONCLUSIONS AND RECOMMENDATIONS

This report considers the main pollutants identified in emissions produced during the combustion of sewage sludge and chemical, clinical and municipal wastes. It uses two separate methods to rank the pollutants in order of priority. The first uses a modelling approach to set priorities on the basis of the estimated impact of incinerator emissions on background exposures. The second approach ranks the pollutants on the basis of their potential health effects.

The pollutants from both lists have been compared and amalgamated into one priority list of ten individual pollutants or groups of pollutants.

The final list comprised five metals (mercury, cadmium, arsenic, chromium and nickel), three groups of organic compounds (dioxins, PCBs and PAHs), SO_2 and PM_{10}. The report reviews the main health effects of these pollutants, paying particular attention to effects at low levels of exposure. In addition, epidemiological studies of both incinerator workers and individuals living near incinerators are reviewed to assess the reported health effects in these populations.

Generally, few data are available on the human health effects of low levels of exposure to the key pollutants; most information comes from occupational studies or environmental accidents, both of which generally relate to much higher levels of exposure. In addition, the data for these pollutants usually relate to exposure to a single chemical or group of chemicals; data concerning health effects resulting from exposure to mixtures are not available.

Many of the ten pollutants are classified as carcinogenic by at least one national or international authority. The evidence for these classifications comes mainly from studies of occupationally- or accidentally-exposed individuals exposed to relatively high levels, or from animal investigations. Epidemiological evidence for (or against) the carcinogenic risk of these chemicals in humans at environmental levels is largely either absent or equivocal, although this may be due to the inability of epidemiological studies to detect small risks rather than an actual absence of effect.

For the non-carcinogenic effects of the pollutants there are some data showing effects at low levels of exposure. For example, there is some evidence for subtle neurobehavioural effects resulting from low-level exposure to mercury, although the significance of these effects for the general population is not known. For SO_2 and PM_{10} there have been reports of dose-dependent increases in both morbidity and mortality in the general population, particularly in susceptible subgroups, at background levels of exposure.

Generally, however, data on the effects of background environmental exposures are either lacking or of poor quality. It is therefore extremely difficult to assess what impact, if any, a relatively small additional exposure from incinerators may have. It is clear that there is a need for good-quality human exposure data for these chemicals, either from monitoring actual levels of exposure or by using validated modelling techniques, before a thorough risk assessment process can be applied.

A further complication when assessing the risk from incinerator emissions is that people are rarely, if ever, exposed to single chemicals. Instead they are almost always exposed to combinations of chemicals; the health effects of such combinations are, without exception, poorly described. In carrying out a risk assessment for a municipal incinerator, there is therefore a need to identify the most common mixtures of materials released in the emissions, to assess the available health effects data and to develop a toxicological profile for such mixtures, especially over the range of exposures likely to be encountered.

RECOMMENDATIONS FOR FURTHER STUDIES ON EXPOSURE

Two specific recommendations for further research resulted from the workshop.

- The toxicity of many metals depends on which chemical form is present. More information is therefore required on the speciation of metals in the environment, especially nickel and chromium. It is also important to know whether there are differences in speciation between urban and non-urban environments.

- In addition to obtaining good-quality emissions data, more emphasis should be placed on the measurement of personal exposure and the levels of pollutants, including dioxins, in individuals living in the vicinity of incinerators (e.g. by analysing breast milk).

4.2 EVALUATION OF HEALTH EFFECTS ASSOCIATED WITH INCINERATOR EMISSIONS

A few epidemiological studies have analysed mortality (mostly as a result of cancer) in people who work in incineration plants, but no consistent excess incidence of any specific disease has emerged. The ability of such investigations to detect adverse effects, however, is limited by their relatively small size, the difficulty in taking account of potentially confounding exposures such as smoking and socio-economic factors, and uncertainties about the extent of any healthy worker effect. Furthermore, health risks for working adults may be different from those for other groups of the population such as children or the elderly.

Other studies have examined mortality and morbidity in communities living near incinerators. Again, interpretation is complicated by the possibility of confounding, particularly by social deprivation, especially when the observed relative risks are less than 1.5.

A further limitation is the use of distance of residence from an incinerator as an index of exposure. Airborne concentrations of pollutants are determined by variables such as wind speed and direction as well as distance from the point of release, and in any case people often spend much of their time away from their places of residence. Exposure by routes other than inhalation will depend on personal habits such as the consumption of home-grown vegetables. Again, this may not relate to distance from the incinerator in a simple fashion.

Before substantial resources are committed to further studies, there is a pressing need to establish empirically to what extent residence near an incinerator influences personal uptake of pollutants and to identify what other factors are important.

RECOMMENDATIONS FOR FURTHER STUDIES ON HEALTH EFFECTS

Two types of human health investigation may be useful in looking for relations between human health and incinerator emissions. The first would look at cancer, birth defects and respiratory disease rates in areas thought to be affected by releases from incinerators; the second would focus on a particular site or sites of interest or concern. In order to detect small increases in risk with a sufficient degree of statistical confidence, such studies would have to be very extensive.

LIST OF PARTICIPANTS

HEALTH EFFECTS OF THE PRODUCTS OF WASTE COMBUSTION

WORKSHOP HELD AT LEICESTER, UK ON 22 JANUARY 1996

Members

Mr J Beach, McLaren/Hart Environmental Engineering, Atlantic Avenue, Alameda, California, USA

Dr AR Boobis, Clinical Pharmacology, Royal Postgraduate Medical School, DuCane Road, London

Professor J Bridges, Robens Institute, University of Surrey, Guildford, Surrey

Professor P Burney, Department of Public Health Medicine, UMDS, St Thomas's Hospital, London

Dr D Coggon, MRC Environmental Epidemiology Unit, Southampton General Hospital

Professor AD Dayan, DH Department of Toxicology, Medical College of Saint Bartholomew's Hospital, Dominion House, Bartholomew's Close, London

Dr GH Eduljee, Environmental Resources Management, Eaton House, Wallbrook Court, North Hinksey Lane, Oxford

Dr S Harrad, Environmental Health School of Chemistry, University of Birmingham, Edgbaston, Birmingham

Professor R Harrison, Environmental Health School of Chemistry, University of Birmingham, Edgbaston, Birmingham

Professor ST Holgate, School of Medicine, Southampton General Hospital, Temona Road, Southampton

Dr LS Levy, Institute of Occupational Health, University of Birmingham, Edgbaston, Birmingham (Chairman)

Mr AH Mann, Robens Institute, University of Surrey, Guildford, Surrey

Mrs J Petts, Centre for Hazard & Risk Management, Loughborough University of Technology, Ashby Road, Loughborough

Dr D Purser, Fire Research Station, BRE, Bucknalls Lane, Garston, Watford

Dr A Smith, MRC Toxicology Unit, Hodgkin Building, University of Leicester

Mr MC Thorne, Electrowatt Engineering Services (UK) Ltd., North Street, Horsham, West Sussex

Representatives

Mr S Aumônier, Wastes Resources Department, ETSU, Harwell, Didcot, Oxon

Mr AG Bond, HMIP, Romney House, Marsham Street, London

Mr P Dyke, Wastes Resources Department, ETSU, Harwell, Didcot, Oxon

Dr J McNamara, MRC Head Office, 20 Park Crescent, London

Dr RL Maynard, Department of Health, Skipton House, 80 London Road, London

Dr P Miller, MAFF, Nobel House (Ergon House), 17 Smith Square, London

IEH Secretariat

Mr K Amaning
Dr D Gompertz
Dr P Harrison (Head of Environmental Toxicology and Programme Management Group)
Dr C Humfrey
Dr L Shuker (Head of Publications and Information Unit)
Dr M Taylor

Technical assistance

Mrs P Forster
Miss S Howe

Acknowledgements

Dr S Harrad and Prof R Harrison for the identification of key pollutants and the identification and assessment of routes of exposure

Charles Butcher for editorial services

IEH PUBLICATIONS

IEH Reports

Air Pollution and Health: Understanding the Uncertainties
Report R1 published 1994

Air Pollution and Respiratory Disease: UK Research Priorities
Report R2 published 1994 (out of print)

Natural and Man-Made Mineral Fibres: UK Research Priorities
Report R3 published 1995

Perinatal Developmental Neurotoxicity
Report R4 published 1996

The Use of Biomarkers in Environmental Exposure Assessment
Report R5 published 1996

IEH Assessments

Environmental Oestrogens: Consequences to Human Health and Wildlife
Assessment A1 published 1995

Indoor Air Quality in the Home: Nitrogen Dioxide, Formaldehyde, Volatile Organic Compounds, House Dust Mites, Fungi and Bacteria
Assessment A2 published 1996

Oilseed Rape: Allergenicity and Irritancy
Assessment A3 published 1997

Special Reports

Understanding Asthma published 1995

Health Effects of Ozone and Nitrogen Dioxide in an Integrated Assessment of Air Pollution published 1997

For further details please contact:

IEH, University of Leicester, 94 Regent Road, Leicester LE1 7DD, UK
Phone 0116 223 1600 Fax 0116 223 1601