

WHO/SDE/OEH/01.3
English only
Distr.: Limited

HUMAN EXPOSURE ASSESSMENT

An Introduction

Marika Berglund
Carl-Gustaf Elinder
Lars Järup

©World Health Organization, 2001

This document is not issued to the general public and all rights are reserved by the World Health Organization. The document may not be reproduced or translated, in part or in whole, without the prior written permission of WHO.

The views expressed in documents by named authors are solely the responsibility of those authors.

The illustrations of the cover page are from the WHO photo library.

The Swedish Environment Protection Agency financed the printing of this textbook. The text is available at the web site of The Institute of Environmental Medicine, Karolinska Institutet, Stockholm <http://ki.se/IMM>

Preface

This book is part of a World Health Organization (WHO) series on teaching material and provides an introduction to the basic principles and methods of human exposure assessment. It constitutes a complement to Basic Epidemiology by Beaglehole et al (1993), and to Environmental Epidemiology (Baker et al, 1999), previously published by WHO. The textbook is intended for use in training courses, but also includes some fundamental information for the interested reader. The target groups are:

- Environmental medicine and epidemiology students
- Environmental and occupational health professionals
- Risk management professionals
- People with a basic knowledge of environmental health and epidemiology
- Chemists, engineers and students of life-sciences

The purpose of this book is to present basic knowledge about human exposure assessment and how it relates to other scientific specialities involved in public health protection. The overall aim of human exposure assessment is to promote and protect public health. It comprises all the methods available to describe, estimate and determine, qualitatively and quantitatively, people's contact with hazardous agents. The character of exposure assessment is multidisciplinary and therefore involves experts from various fields of science. Human exposure assessment plays an important role in epidemiology, risk assessment and risk management, as well as in status and trend analysis. The science of human exposure assessment is a growing field and this textbook offers references to more in-depth books and reviews which are provided at the end of this book (Chapter 10: Continuing your education).

The World Health Organization and the United Nations Environment Programme (UNEP) have been promoting improved human exposure assessment through various activities for more than 20 years. One of these activities was the Human Exposure Assessment Location (HEAL) project which was implemented by WHO and UNEP with support from US EPA, the Japanese Government and other national agencies and which ran for more than 10 years (UNEP/WHO, 1986). The HEAL project was initiated to promote international collaboration in development and harmonisation of exposure assessment methodology and quality assurance activities.

In 1995, in response to the recommendations from the United Nations Conference on Environment and Development (UNCED) held in Rio de Janeiro 1992, the HEAL project was reorientated. The emphasis is now on the preparation of training and promotion material with the aim of teaching appropriate methods and technologies to assess human exposure.

Human Exposure Assessment. An Introduction has been prepared with a view to strengthening education, training and decision-making in the field of public health. The first draft of the book was discussed during a joint Workshop on Human Exposure Assessment in Environmental Health Decision-making in November 1996, arranged by the WHO and the Institute of Occupational Medicine and Environmental Health in Sosnowiec, Poland. The final draft was discussed during a meeting in Stockholm in November 1998.

The authors gratefully acknowledge the valuable contributions received from a large number of colleagues:

Dr Tom Bellander, Department of Environmental Medicine, Stockholm County Council, Stockholm, Sweden

Dr Kersten Gutschmidt, Occupational and Environmental Health, Department for the protection of the human environment, WHO, Geneva, Switzerland

Prof. Vladimír Janout, Department of Preventive Medicine, Palacky University, Olmouc, Czech Republic

Prof. Tord Kjellström, Department of Community Health, University of Auckland, Auckland, New Zealand

Dr Nino Künzli, Institute of Social and Preventive Medicine, University of Basel, Basel, Switzerland

Dr David MacIntosh, Environmental Health Sciences, University of Georgia, Athens, Georgia, USA

Prof. Astrid Saava, Department of Public Health, University of Tartu, Tartu, Estonia

Dr Andrew Taylor, Robens Institute of Surrey, University of Surrey, Guildford, United Kingdom

Dr Renata Zlotkowska, Institute of Occupational Medicine and Environmental Health, Sosnowiec, Poland

We also thank *Ms Barbro Rahnster*, *Ms Anna Persson*, *Dr Britt-Marie Bäcklin* and *Dr Ann Thuvander* for preparation of original figures and finalisation of the manuscript.

The authors would like to encourage readers to provide comments, suggestions, and technical corrections. Communications can be sent to:

Dr Marika Berglund
Institute of Environmental Medicine, Karolinska Institutet
Box 210
SE-171 77 Stockholm
Sweden
e-mail: Marika.Berglund@ki.se

CONTENTS

1 THE CONTEXT OF HUMAN EXPOSURE ASSESSMENT	1
The origin of human exposure assessment	1
The role of human exposure assessment in public health	3
Developments in human exposure assessment	11
2 DEFINITIONS AND KEY CONSIDERATIONS	15
Definitions of exposure	15
The environment-health chain	18
Sources and emissions	18
Transport, transformation and fate	18
Exposure pathways and routes	20
Dose	21
Toxicokinetics	22
The relationship between exposure or dose and health effects	23
The scope of human exposure assessment	24
Key considerations of human exposure assessment	25
Time and location	25
Additional factors modifying exposure and dose	29
Exposure distributions and high-risk groups	32
3 APPLICATIONS	35
Occupational and environmental epidemiology	36
Exposure assessment in various types of epidemiological studies	38
Risk assessment and risk management	44
Risk assessment	44
Risk management	47
Status and trend evaluation	49
4 STUDY DESIGN AND STRATEGIES	51
Different approaches to human exposure assessment	51
Planning a human exposure assessment study	53
Study population	55
Study plan	57
Data preparation	58
Pilot study	59
Limitations and sources of errors in human exposure assessment	60

5 METHODS OF ASSESSING EXPOSURE AND DOSE	65
Questionnaires	65
Questionnaire design	66
Types and contents of questions	68
Question language and format	68
Questionnaire structure	69
Time-activity data	69
Using questionnaires	70
Using diaries	70
Environmental monitoring	70
Air	72
Food	74
Drinking-water	75
Soil	76
Dust	77
Microorganisms and biological particles	78
Personal monitoring	79
Air	79
Food and drinking-water	81
Ingestion of non-food substances	83
Dermal exposure	84
Ionising radiation	85
Biological monitoring	85
Biomarkers	86
Common media used in biological monitoring	87
Other human media that can be used for biological monitoring	92
Modelling exposure	94
Geographic Information Systems (GIS)	98
6 DATA QUALITY	101
Definitions and scope of quality assurance and control	101
Pre-analytical quality control	102
Analytical quality control	102
Analytical quality control samples	103
Reference materials	104
Commercial external quality assessment schemes	105
Record-keeping and data validation	105

Record-keeping and data validation	105
Sources of variation in analytical results	108
Collection of samples	108
Handling and storage of samples	108
Gross errors	109
Analytical variation	109
Analytical method selection	112
7 DATA ANALYSIS AND PRESENTATION	115
Choice of statistical methods	115
Description of data	117
Data analysis	120
Sensitivity analysis	121
8 ETHICAL CONSIDERATIONS	123
9 FIELD EXAMPLES OF DIFFERENT EXPOSURE SITUATIONS	127
Introduction to field examples	127
Air pollution and respiratory morbidity in Delhi, India	129
Example of a questionnaire	136
A cross-sectional total exposure assessment study of lead in children of Mexico City	139
Assessment of pesticide exposure in epidemiological studies in Costa Rica	145
Industrial setting - The Rönnskär case	151
A major chemical accident - The Bhopal Disaster	157
The German Environmental Survey (GerES)	163
10 CONTINUING YOUR EDUCATION	171
Abbreviations	175
Index	177
References	185

List of figures

- Figure 1:** Decreasing concentrations of carbon disulphide (mg/m^3) in workroom air and the corresponding risk reduction of ischemic heart disease (data from Hernberg and Nurminen, 1985) 7
- Figure 2:** Blood lead concentrations in children living in the vicinity of a smelter situated 1 km from the town centre of Landskrona (*near smelter*, 0.5-1 km from smelter), in the urban area of Landskrona (*other urban area*), and in the *rural area* of Landskrona (data from Strömberg et al, 1995) 10
- Figure 3:** Humans are exposed to chemical pollutants, as well as physical and biological agents, at home, at work, in the community and in the general environment. Personal (receptor-oriented) exposure assessments take into account all the different sources and locations of exposure 12
- Figure 4:** The relationship of environmental concentration, exposure concentration, and dose, as well as factors that influence the exposure and dose 17
- Figure 5:** The environment health chain: the relationship of source activities, environmental concentrations, exposure, dose, and health effects (adapted from Briggs et al, 1996) 19
- Figure 6:** The relationships of environmental and exposure media, and exposure pathways and routes. Bold arrows indicate one example of an exposure pathway (adapted from McKone and Daniels, 1991) 22
- Figure 7:** An example of a dose-effect relationship, as the dose increases so does the degree of effect, from slight headache to death (Beaglehole et al, 1993) 23

Figure 8: Relationships between dose or exposure and prevalence in percent (response) of individuals, as the dose or exposure increases, so too does the prevalence of individuals experiencing minor dysfunction, minor effects and major effects (response), from a few to almost 100 percent (Elinder et al, 1994) 24

Figure 9: Two individuals experiencing different exposure patterns but the same cumulative dose. During the time period shown subject A encountered considerably higher concentration of the pollutant than subject B, but the cumulative exposure (area under the curve) was the same for both individuals 26

Figure 10: Example of day-to-day variations of NO₂ exposure (µg/m³) in relation to activities for two children: one living in an urban area (left) and one living in a rural area (right). Notice the ten-fold difference on the y-axis. *Left:* On Monday this child went skating for 2 h in the indoor ice-skating arena. Saturday she spent 3 h in the downtown area, indoors (2 h) and outdoors (1h). Sunday was spent at home. *Right:* Wednesday (1.5 h) and Sunday (2 h) were spent in the indoor ice-skating arena by this boy (data from Berglund et al, 1994b) 28

Figure 11: Intake of cadmium via different types of diets (medians and 95-percentiles, µg Cd/10 MJ; data from Berglund et al, 1994a; Vahter et al, 1996) 30

Figure 12: Physiological model estimated tissue concentrations of ethylene oxide in the three major tissue groups for two identical periods of inhalation exposure but different levels of exercise (adapted from Åstrand et al, 1983) 33

Figure 13: Hypothetical exposure distributions illustrating the relationship between the general population and population subgroups (adapted from Sexton et al, 1995) 33

Figure 14: Concentrations of some organochlorine contaminants in human milk 1972-1992 (data from Lundén and Norén, 1998)	50
Figure 15: Different approaches to human exposure assessment (adapted from NRC 1991b)	52
Figure 16: Trend of decreasing concentrations of some air pollutants in Stockholm 1980-1995	72
Figure 17: Estimated adjusted mortality rate ratios in six US communities in relation to concentrations of fine particles in air (data from Dockery et al, 1993)	73
Figure 18: Urine concentrations of β -2-microglobulin versus mercury (U-Hg), unadjusted and adjusted. Without adjustment for dilution of urine (left figure) there was a significant but erroneous correlation between urinary excretion of mercury and β -2-microglobulin (data from Langworth et al, 1992)	90
Figure 19: Excretion of cobalt in urine in a group of hard-metal workers, before and after their work-shift, during one workweek and the following weekend (Elinder et al, 1994)	92
Figure 20: Example of the Shewhart chart. A) Data in control about the target value. B) Data offset from the target value. C) Drifting data. D) Data with a steep change (Prichard, 1995)	107
Figure 21: Graphical illustration of accuracy and precision	109
Figure 22: Illustration of the ideal case and various types of bias (for explanation see text; UNEP/WHO, 1986). The dotted line illustrates the ideal line $y=x$	110
Figure 23: Illustration of random analytical variability (for explanation see text; UNEP/WHO, 1986)	112

Figure 24: A logarithmic transformation of data can produce a normal distribution	116
Figure 25: A histogram presentation of urinary cadmium concentrations in a group of cadmium exposed workers. The smooth curve approximates the distribution (data from Järup and Elinder, 1994)	118
Figure 26: A box plot presentation of the same data presented in figure 25	118
Figure 27: Prevalence of dyspnoea, cough, and forced expiratory flow (FEF) in relation to distance to the factory (data from Cullinan et al, 1997)	161
 List of boxes	
Box 1: Disease outbreaks associated with environmental pollution	3
Box 2: Guidelines and standards	5
Box 3: Examples of indoor sources of exposure	11
Box 4: Relationship between environmental concentration, exposure, absorbed dose, target organ dose and biologically effective dose: Lead as an example	21
Box 5: Time activity data	28
Box 6: Example of a confounder that should be considered and quantified	29
Box 7: Intake of contaminated fish gave rise to developmental effects in children	31

Box 8: Cumulative cadmium exposure and prevalence of kidney dysfunction	39
Box 9: A case-control study of lung cancer in Stockholm	41
Box 10: The Cadmibel study	42
Box 11: Determination of a threshold value or NOEL, and its use in calculating an acceptable daily intake, ADI	47
Box 12: Adjustment of urine samples	89
Box 13: The time-weighted integrated exposure model	97
Box 14: Some sources of reference materials with general coverage	104
Box 15: Some examples of EQAS extending their services world-wide	105
Box 16: Quantitative estimation of analytical precision	113
Box 17: An example of a basic sensitivity analysis	122
Box 18: Informed consent	125

List of tables

Table 1: Examples of various types of potentially harmful agents	13
Table 2: Differences between occupational and environmental exposure assessment	37
Table 3: Exposure-response relationship between cumulative exposure to cadmium in work room air and the prevalence of tubular proteinuria in Swedish nickel cadmium battery workers (Järup et al, 1988)	40

Table 4: Examples of default values, which can be used in exposure assessment	46
Table 5: Different aspects of the contact between people and pollution that are potentially important when planning a study, and in the following exposure analysis (adapted from Sexton et al, 1995)	54
Table 6: Important requirements for improvement of human exposure information (Graham et al, 1992)	63
Table 7: Strengths and weaknesses with stationary and personal air sampling	80
Table 8: Classification of compounds by elimination half-time, time to reach steady state after continuous exposure and resulting sampling requirements (from Heinzow and McLean, 1994)	91
Table 9: Time spent in different microenvironments with different CO concentrations (WHO, 1982)	96
Table 10: Example of presentation of results (exposure and effect estimates) from a study of cadmium exposed women in Stockholm, Sweden, showing the means and variability. SD=Standard deviation. NAG=N-acetyl- β -D-glucosaminidase	119
Table 11: Standard Mortality Ratios (SMR) computed for different exposure categories. SMR_0 was computed using the original exposure data. SMR_1 was computed using exposures prior to 1940 multiplied by 0.5, and exposures between 1940 and 1950, multiplied by 0.75. CI=confidence interval (Järup, 1992)	122

After reading this chapter you will:

- Be aware of the development and current status of human exposure assessment
- Understand the important role of human exposure assessment in public health
- Recognise the increasing scientific basis for human exposure assessment
- Be aware of the multidisciplinary character of human exposure assessment

The origin of human exposure assessment

Exposure assessment has been an integrated and natural part of human history and civilisation. Different kinds of exposures, and various types of foods and environments, were encountered by the early humans, who soon learnt what could be eaten or not, and what kinds of environments should be avoided. It was also experienced that human senses were not always sufficient to predict what could be eaten, or what environments could be met, without risks of health effects. Wild growing berries sometimes proved to be poisonous. During the Roman period, slaves, convicts, and political enemies who were sent to the mercury mines in Almadén in Spain did not survive long due to exposure to mercury vapour that they could not perceive. From harsh experiences humans thus learnt that certain types of foods and environments should be avoided, if possible.

Exposure assessment aims at prevention. Early professionals in the field of exposure assessment were the tasters at the court of the Roman Emperors. They had to consume part of the food to be served to the Emperor in order to reveal if the meal was poisonous or not - if they survived, the meal was obviously not poisoned, and it was safe for the Emperor to eat it. The Italian

physician Bernardino Ramazzini (1633-1714) took a more scientific approach. He was the first to realise, and report, that there were associations between occupation, exposure and particular diseases. Ramazzini realised that specific exposures occurring in different occupations may cause the disease. Smoke and white glowing iron gave the blacksmith sore and inflamed eyes. Potters became anaemic and suffered from palsies from exposure to lead salts used for glazing.

John Snow (1813-1858) in London in the 1850s noted the apparent association between the source of drinking-water and the risk of dying from cholera. Although Snow was never able to see the cholera bacteria, he understood that the disease was caused by exposure to a disease-causing agent in drinking-water.

Anoxia from odourless carbon monoxide in coalmines is a well-known hazard for miners. Canary songbirds were introduced for monitoring the air quality in the British mines in the 18th Century. If the miners observed that the canary suddenly lay dead in the bottom of the cage, they knew that they should leave the mine immediately in order not to get killed by carbon monoxide. Birds have a much higher basal metabolism than humans and are thus intoxicated faster than humans from carbon monoxide. Canaries were kept in British mines until recently.



At the end of the 19th and the beginning of the 20th Century, there was considerable interest among health professionals in the associations between environmental factors and disease. However, when knowledge about the role of bacteria was obtained, and antibiotics became available, the interest of most health professionals, in particular physicians, moved from prevention to treatment.

The role of human exposure assessment in public health

Eventually, the interest moved from treatment to prevention again. In the 1950s and 1960s, the systematic analysis of occupational exposure and health effects began. At the same time a series of disease outbreaks that were associated with environmental factors, such as the London fog episode and the Minamata Disease, drew attention to relationship between environmental hazards and the health of human communities (Box 1). This brought a renaissance to the realisation of the importance of environmental factors for the development of diseases. Since then, the need for environmental protection and awareness of the links between environmental protection and human health have been subject to growing concern and increasing interest among health professionals, politicians and the public.

Exposure assessment is crucial for the identification, evaluation and control of health risks in the workplace as well as in the general environment. The basis for the control of health risks is guidelines and standards (Box 2, p. 5).



Disease outbreaks associated with environmental pollution

The London fog episode

During a week of unusually severe fog in London in December 1952, a several-fold increase in deaths from lung and heart diseases was registered. The atmospheric conditions resulted in a temperature inversion, which can be compared to a lid being placed on top of the city. Air pollutants were concentrated under this lid. Routine measurements of ambient air concentrations of sulphur dioxide and total suspended particulate (TSP) at that time made it possible to conclude a close relationship between the increased morbidity and mortality, and the exposure to air pollutants.

Mercury poisoning of the general populations in Japan and Iraq

Epidemics of accidental methylmercury poisoning occurred in Minamata and Niigata, Japan in the 1950s and in Iraq in

cont.

1955, 1960 and 1972.

Intake of methylmercury causes neurological symptoms such as sensitivity disturbances, ataxia, impairment of speech, constriction of the visual field and hearing loss. Prenatal exposure causes psychomotor retardation, and in severe cases un-specific infantile cerebral palsy.

When metallic mercury, used as a catalyst in the acetaldehyde plant near Minamata Bay, was discharged into the bay as waste sludge, the aquatic plant life converted the metallic mercury to methylmercury. This methylmercury was taken up by the fish and shellfish and the local inhabitants, many of whom were fishermen, were poisoned by the contaminated seafood (Tsubaki and Irukayama, 1977). The neurological syndrome that affected the people in the area was called the Minamata Disease.

In Iraq, seed grain treated with an organomercurial antifungal agent was used by peasant farmers to make bread during years of bad crop. Intake of the contaminated bread caused epidemics at multiple sites (Bakir et al, 1973). The relationship between health risks and intake of methylmercury has been developed from data mainly obtained from studies of these epidemics.

The role of human exposure assessment in occupational health

Hazardous agents in the occupational setting, such as asbestos, radon, soot, metals and benzene, were first recognised to cause health effects among workers. Despite rather crude methods for measuring exposure, it was possible to link exposures with observed health effects since the excess risks were large.

Increasing sensitivity of measurement equipment and the development of personal monitors for measuring exposure to air pollutants on the individual level have made it possible to detect hazardous agents at much lower concentrations than before and also to follow up changes of exposure over time and to link human exposures with various health effects. This has resulted in decreased standards for occupational exposures in many countries.

A study from Finland on carbon disulphide exposure and risk for cardiovascular disease shows the impact on workers' health after monitoring and reducing the exposure to a hazardous substance at the workplace (Nurminen and Hernberg, 1985). The initial evidence for the cardiovascular disease risk from carbon disulphide exposure was provided in an epidemiological study published in 1970. Because exposure control measures had been gradually improving over the years up to 1970, no new action was taken until a 5-year follow-up study demonstrated persistence of the excess risk of death from cardiovascular disease. New and intensive control efforts were

Guidelines and standards

The primary aim of guidelines and standards is to protect human health in the occupational as well as in the general environment, and to eliminate or minimize exposure to hazardous agents. The guideline values are based on scientific evaluation of existing data such as toxicological and epidemiological data, and most often include expert judgement. An adequate margin of safety should exist between the guideline values and the concentrations at which toxic effects will occur. The guideline values are intended to give background information and guidance to governments and regulatory authorities in making risk management decisions, particularly in setting standards, but their use is not restricted to this.

Governments and regulatory authorities set standards. Before standards are adopted, guideline values (if available) and additional human health information must be considered in the context of prevailing exposure levels and environmental, social, economic and cultural conditions, as well as technical feasibility.

An occupational standard is the administrative limit for the allowable concentration of a hazardous agent that is handled or produced in an occupational setting (for example, concentrations of organic solvents in workroom air), for protection of workers' health. Repeated measurements have to be carried out in the regulated occupational setting for compliance with the occupational standards.

Environmental quality guidance values such as the WHO Air Quality Guidelines (WHO, 1999) and the WHO Guidelines for Drinking-Water Quality (WHO, 1993; 1996a; 1998 a,b) provide a basis for protecting the general population from adverse effects of environmental pollutants. Environmental quality guidelines assist governments to carry out local control measures in the framework of environmental quality management. For example, air quality guideline values are levels of air pollution below which lifetime exposure or exposure for a given average time does not constitute a significant health risk; short-term excess do not mean that adverse effects automatically occur; however the risk of such effects increases. Of course, guideline values and standards should not be regarded as implying that the quality of that medium may be degraded to the recommended or legally binding level. Indeed, a continuous effort should be made to maintain media quality at the highest level possible.

More information on WHO environmental quality guidelines and standards is available on the WHO web site (<http://www.who.int>).

initiated and 10 years later a further follow-up study was undertaken. The results showed dramatic evidence of risk reduction (Figure 1). The authors suggested, in fact, that the fraction of prevented or postponed cardiovascular deaths among the exposed workers was in the order of 70 %.

Measuring hazardous agents in workroom air, and keeping air concentrations below permissible standards, is not always sufficient for protection of workers' health. In heavily contaminated industrial settings, workers are exposed to hazardous substances not only via the respiratory system, but also via the gastrointestinal tract due to contamination of food, cigarettes etc., leading to peroral exposure (intake via the mouth). It is not unusual for workers to eat their food at the workplace without having time to wash their hands, thus getting dust from the environment on the food. For some chemicals, such as organic solvents and pesticides, dermal exposure and uptake through the skin can contribute substantially to the received dose. Workers wearing protective clothing may also be exposed due to inadequacy of the protective gear, for example gloves that do not prevent organic solvents from penetrating, leading to dermal exposure and uptake through the skin. By the use of biological monitoring (Chapter 5, p. 85), that is, measurements of hazardous agents in human biological media such as blood or urine, it has been possible to measure the total exposure, and the resulting dose, to a specific agent from inhalation, intake via the mouth and dermal uptake. It has been demonstrated that there are great differences in actually received doses among workers, due to variations in personal habits and activities. Analyses of blood and faeces of workers exposed to metal dust have shown that industrial exposure often takes place both through inhalation and ingestion (Hassler, 1983). If the workplace is contaminated with dust it can be expected that workers' hands, foods and cigarettes will also be contaminated, and dust thereby reaches the mouth of the worker.

The role of human exposure assessment in environmental health

The severe fog period in London, in 1952 (Box 1, p. 3), showed that exposure to air pollutants was indeed not merely a problem within the factory walls (United Kingdom Ministry of Health, 1954). Measurements of ambient air pollutants have routinely been carried out in many countries for several decades, with the purpose of monitoring air quality. The data acquired make it possible to study

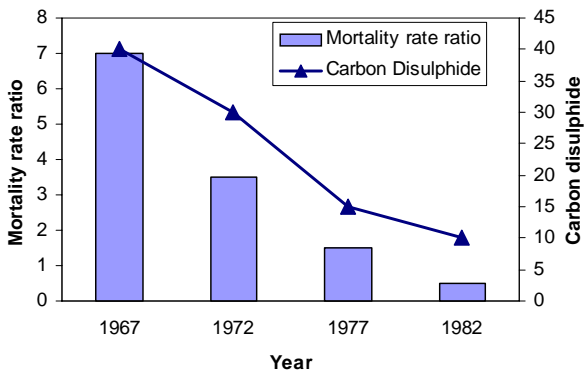


Figure 1. Decreasing concentrations of carbon disulphide (mg/m^3) in workroom air and the corresponding risk reduction of ischemic heart disease (data from Hernberg and Nurminen, 1985).

status and trend of some common air pollutants. In general, stationary air monitors are located in urban areas, often several metres above ground, and often in highly polluted spots. Based on these data, ambient air standards have been established (Box 2, p. 5).

In 1974, the Global Environment Monitoring System (GEMS/Air) was implemented by the United Nations Environment Programme (UNEP) and the World Health Organization (WHO). GEMS/Air was later renamed to Air Monitoring Information System (AMIS). Through AMIS, internationally comparable urban air pollution data are collected in about 100 cities of 40 countries from different parts of the world. Generally, sulphur dioxide (SO_2) and total suspended particulate (TSP), and more recently carbon monoxide (CO), nitrogen oxides (NO_x), and lead (Pb), are monitored in three stations of each city, representing industrial, commercial, and residential zones.

The techniques used for exposure assessment in the occupational setting are also applicable to the general environment. In many cases, monitoring techniques used in industrial hygiene have been modified to enable studies of human exposure in the community environment. For example, sensitive personal air monitors that are able to measure environmental concentrations of air pollutants in

the "breathing zone" of an individual have become available (Chapter 5, p. 79). Biological monitoring has also been used in studies of the general population, especially in studies of exposure to metals such as lead, cadmium, and mercury.

Environmental exposures are generally more complex to assess than occupational for various reasons, such as:

- Concentrations of pollutants are usually much lower in the general environment than in the occupational environment, which requires more sensitive measurement techniques
- In the occupational setting, there are usually well-defined groups of people who are exposed, often healthy male workers, while the general population includes children, the elderly and people with different diseases, who may be more susceptible to exposure and effects
- In the occupational setting there is generally a limited set of hazardous agents to be considered, while in the general environment there is often a variety, and a mixture, of potentially hazardous agents to be examined
- Workers are exposed within a reasonably well-defined occupational setting, while the general population is exposed in different environmental settings with various concentrations, outdoors and indoors, in urban and rural areas, and at home, school or work, etc.
- The general population is exposed intermittently throughout a whole lifetime, over periods of days, months, years, or decades, whereas a worker is exposed during working hours. Of course, the worker is also a member of the general population

Thus, exposure assessment in the general population usually deals with long-term, low-level exposure in many different environmental settings compared to occupational exposure assessment which is characterised by short to medium-term, medium to high level exposure in relatively well-defined settings.

One example of environmental health achievement in the control of environmental exposures is possibly the decrease in lead exposure in the general population due to the reduction of lead in petrol and the introduction of unleaded petrol. Health risks resulting from lead pollution of the general environment have been extensively discussed in the last decade. The debate has especially focused on the health risks (neurobehavioural effects) to young children and foetuses. One of the major achievements by environmental exposure assessment studies has been to clearly establish the association between environmental lead pollution and the actual received dose in humans.

Lead is a multimedia element, present in ambient air, drinking-water, food, soil and dust, and human exposure may originate from many different environmental sources. In recent years a number of measures have been introduced to decrease exposure to lead in the general population of many countries.

In Sweden, legislation against lead in petrol lowered the highest permissible level from about 0.80 g/l in 1963 to 0.15 g/l in 1981. Unleaded petrol has been available at most filling stations since 1987 and today, leaded petrol has been almost totally phased out. From 1978 to 1994, yearly blood samples were collected from children in schools and nurseries in the area of Landskrona in the south of Sweden (Strömberg et al, 1995). Since 1944, there has been a secondary lead smelter located about 1 km from the town centre. In 1984, another secondary lead smelter was built close to the first one. The children were divided into three groups according to their residence area: near the smelter (0.5-1 km from the smelter and urban area), other urban area and rural area. There was a remarkable decrease in blood lead levels during the study period, irrespective of place of residence, as shown in Figure 2 (p.10). Thus, the blood lead decrease should mainly be attributed to a factor that affected all the children, most likely a decrease in the lead concentration in ambient air. A probable cause of the decreased air lead pollution was the extensive reduction in lead emissions from automobile exhausts due to the reduction in the use of leaded petrol. And indeed, the decrease in blood lead concentrations followed the decrease in petrol lead (tonnes) sold in Sweden during the same time period, from 1400 tons of petrol lead in 1978 to 100 tons in 1993. At the same time the airborne “import” of lead pollution from traffic and industry in other parts of Europe decreased. The results from rural areas indicated that the impact of traffic lead was manifested in both rural and urban areas. The reason may be that there was indirect/secondary exposure via

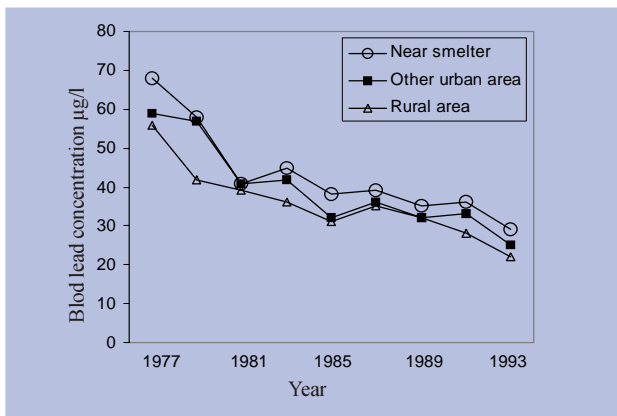


Figure 2. Blood lead concentrations in children living in the vicinity of a smelter situated 1 km from the town centre of Landskrona (*near smelter*, 0.5-1 km from smelter), in the urban area of Landskrona (*other urban area*), and in the *rural area* of Landskrona (data from Strömberg et al, 1995).

food due to contamination, and that most foodstuffs consumed in both urban and rural areas are not grown locally. Therefore, the effect is not dependent upon the area of residence.

Several other studies on the relationships between use of lead in petrol and lead exposure measured as blood lead level have been published. These studies verify the finding that reductions in petrol lead levels have been a major causal factor in the observed reductions in population blood lead levels (Thomas et al, 1999). A decrease in the use of lead in petrol and, consequently, decreased lead emissions to the atmosphere is probably the most important contributory factor to decreased exposure. The results from these studies show clearly the beneficial public health effects of the legislation against lead in petrol.

Developments in human exposure assessment

The science of human exposure assessment has become substantially more complex over the past decades as the demand for relevant and accurate human exposure information has increased in all the scientific fields related to public health protection. It has become more and more obvious that human exposure data must be collected and processed in a standardised manner in order to improve information on exposure. The number of potentially harmful agents has increased enormously during recent decades (Table 1, p.13). However, knowledge and awareness of occupational and environmental exposures as causes of human disease have increased the possibilities for its prevention.

Traditionally, measurements of human exposure to environmental pollutants have focused on industrial point source pollutants and their concentrations in environmental media, most often the concentrations of sulphur dioxide, nitrogen dioxide and soot in ambient air.

For certain chemicals, however, industrial point sources make negligible contributions to human exposures, whereas indoor sources of pollutants may be of much greater importance (Box 3). Furthermore, many people spend a majority of their time indoors. Thus, human behaviour and activity may influence exposure substantially. Development of equipment and methods for measuring individual exposure (for example, personal air monitors) and dose (for example, biological monitoring of lead in blood) in the general population have made it possible to move from source-oriented to receptor-oriented exposure assessment, and the concept of humans as receptors for environmental pollutants has been established (Figure 3, p.12). Receptor-based approaches to human exposure assessment are designed to determine if individuals are actually exposed to hazardous agents, at what level, and from what activities or sources. For effective pollutant control and exposure reduction, the most significant exposure sources and situations have



BOX 3

Examples of indoor sources of exposure

- Gas stoves and other fossil-fuelled furnaces for cooking and heating
- Building materials – evaporation of volatile compounds
- Environmental tobacco smoke (ETS)
- Particles and dust
- Pesticides and other household chemicals
- Consumer products

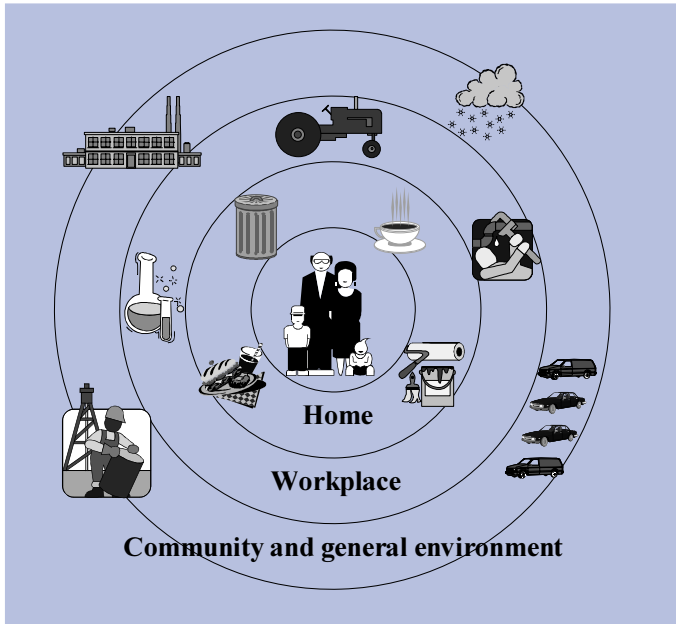


Figure 3. Humans are exposed to chemical pollutants, as well as physical and biological agents, at home, at work, in the community and in the general environment. Personal (receptor-oriented) exposure assessments take into account all the different sources and locations of exposure.

to be identified. If not, pollutant control activities may be misdirected, leading to high costs without any substantial exposure reduction. Individual exposure data combined with activity information, have provided more information on personal and activity-related exposure to air pollutants.

It is often not practical to measure exposure for every person in a population. Therefore, there is a need to collect exposure information that can be used to model exposure in larger populations. Models may allow for extrapolation from relatively few measurements to estimates of exposures and doses for a much larger population (NRC, 1991a). Monitoring data should be used to validate modelled exposures, to ensure that the modelled data accurately reflect the real personal exposures.

Table 1. Examples of various types of potentially harmful agents.

Type of agent	Examples
General chemicals produced in industries and released to the environment	Food additives, pesticides, pharmaceuticals and chemicals
Hazardous agents formed in the environment: <ul style="list-style-type: none"> • In combustion processes • By chlorination of drinking-water • In atmospheric reactions 	Nitrogen dioxide, sulphur dioxide, particulate matter Trihalomethanes Ozone
Biological agents	Bacteria, fungi, allergens from mites and pollen
Physical agents	Noise Radiation: <ul style="list-style-type: none"> • Ionizing radiation Radon • Non-ionizing radiation UV light

Biochemical indicators of exposure and dose, biomarkers, are increasingly being used in exposure assessment. Biomarkers integrate exposures from all sources and pathways. Thus, biomarkers are usually not source specific so it is not possible to determine which source contributed the most to the total exposure. Concerns relating to the chemical specificity of biomarkers, the ability to detect the markers at environmental levels and baseline variability in the general population have been raised (NRC, 1991b). An understanding of the mechanisms underlying the interaction of chemicals with biological systems is necessary for the development of effective biomarkers. An understanding of the relationship between biomarkers and disease is also important.

Important requirements for improvement of human exposure information are outlined in Chapter 4.

Intentionally blank

After reading this chapter you will:

- Be familiar with the definitions of exposure
- Realise the difference between exposure source, environmental concentration, exposure concentration and dose
- Recognise how chemical and physical properties are important for transport and fate of chemical pollutants
- Understand how exposure and dose are influenced by interacting factors

Definitions of exposure

The key word in the definition of exposure is contact. People are in contact with, exposed to, potentially harmful chemical, physical and biological agents in air, food, water, soil, dust, products, etc. Exposure does not result only from the presence of a harmful agent in the environment. There must be contact between the agent and the outer boundary of the human body, such as the airways, the skin and the mouth.

Exposure may be defined as “the contact of a chemical, physical, or biological agent with the outer boundary of an organism”. Exposure is often defined as a function of concentration and time: “An event that occurs when there is contact at a boundary between a human and the environment with a contaminant of a specific concentration for an interval of time” (NRC, 1991b).

There are four important aspects (main characteristics) for determination of exposure:

- | | |
|-----------------------------|----------------------------------------------|
| • The nature of the agent | Chemical, physical and biological properties |
| • The intensity of exposure | How much (concentration) of the agent? |
| • The duration of exposure | For how long a time? |
| • The frequency of exposure | How often? |

Exposure is quantified as the concentration of an agent in a medium in contact with the human body, averaged or integrated over time (duration) of contact.

Various time frames of exposure are:

- Short-term exposure Seconds, minutes, hours, days
- Long-term exposure Weeks, months, years, lifetime
- Cumulative exposure Total exposure over a given period of time

One must distinguish between environmental concentration, exposure concentration, and dose (Figure 4). The environmental concentration of an agent refers to its presence in a particular carrier medium (for example, PAH in ambient air), expressed in quantitative terms (for example, $\mu\text{g}/\text{m}^3$). Similarly, the exposure concentration of an agent refers to its presence in its carrier medium at the point of contact (for example, PAH in breathing zone air) expressed in quantitative terms (for example, $\mu\text{g}/\text{m}^3$). Finally, the dose refers to the amount of a pollutant that actually enters the human body, i.e. is taken up through absorption barriers.

The mathematical relationship for exposure as a function of concentration and time can be represented by the equation:

$$E = \int_{t_1}^{t_2} C(t)dt$$

in which E is the intensity of exposure, C(t) is exposure concentration as a function of time, and t_2-t_1 is the duration of exposure (NRC, 1991b).

A number of variables can influence the exposure and dose. These include physiological factors such as age, gender, physical condition, disease and genetics, as well as exposure factors related to human behaviour and activities (for example how much time is spent commuting to work each day), and contact rates (for example how much drinking-water is ingested per day). Exposure factors that can be used to calculate exposure and dose have been summarised by US EPA (1997). Exposure factors are of course also dependant on physiological factors.

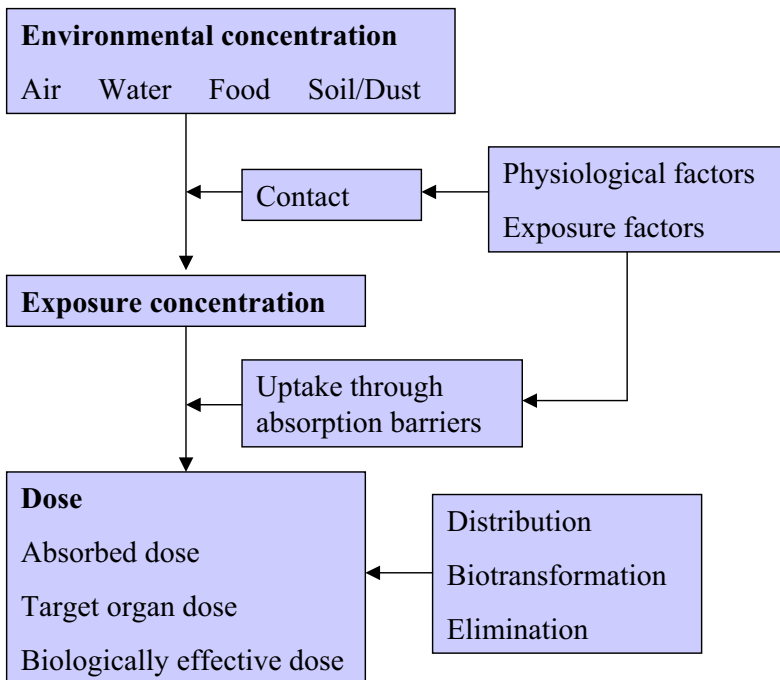


Figure 4. The relationship of environmental concentration, exposure concentration, and dose, as well as factors that influence the exposure and dose.

The environment-health chain

Exposure to potentially harmful agents may lead to a wide range of adverse health effects, ranging from discomfort, dysfunction, injury, and illness (morbidity) to death (mortality). The relationship between source activities, exposure and health effects is illustrated in the environment-health chain (Figure 5).

Sources and emissions

The potentially harmful agents may be natural in origin, for example, emanating from volcanic outbreaks, but the majority derive from human activities and interventions, such as industrial activities, transportation, or energy production. Driving forces are population growth, economic development and technology. There are different types of emission sources, for example point sources such as industries, releasing pollutants to air or water, line-sources such as power-lines and roads, area sources such as run-off from agricultural lands and landfills. Emissions of various pollutants from different sources result in environmental concentrations of pollutants in environmental or carrier media such as air, water, food, soil and dust.

Transport, transformation and fate

The dispersion and eventual fate of the pollutants depends on various factors including the pollutants' physical and chemical properties and on environmental factors such as water-flow and meteorological conditions.

Pollutants are transported over short or long distances, and from one environmental medium to another. The transport of a pollutant in the environment is influenced by a number of factors, including volatilisation and sorption to soil. For example, pollutants with high vapour pressure, such as benzene, will tend to volatilise and partition into the atmosphere. The pollutants may then be moved throughout the atmosphere through air movements or precipitation, or they can re-enter other environmental media through fallout with precipitation (wet deposition) or particulate matter (dry deposition). Pollutants may also sorb to soil particles. They may then be transported through soil erosion, or be taken up by

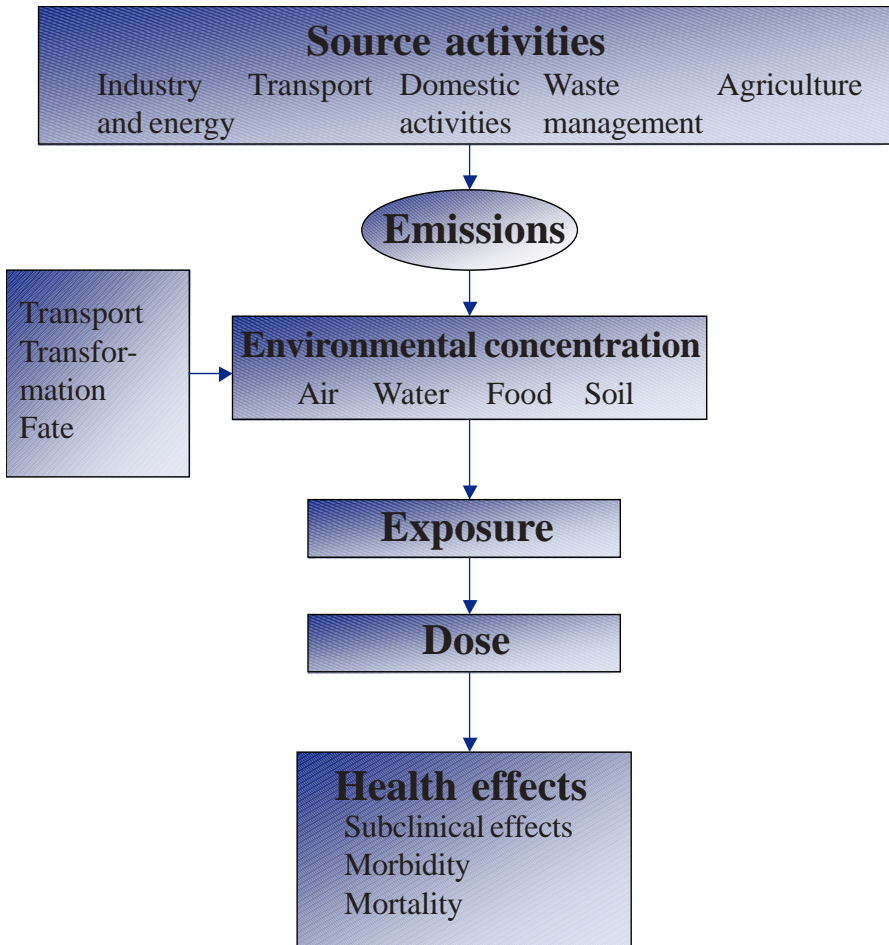


Figure 5. The environment health chain: the relationship of source activities, environmental concentrations, exposure, dose, and health effects (adapted from Briggs et al, 1996).

plants. The adsorption to soil particles can be expressed as an adsorption coefficient (K_d), the extent to which an organic chemical partitions between a solid phase (for example soil or sediment) and a liquid phase (for example water). For example, the K_d is expressed as the mass of the chemical (in mg) adsorbed per unit mass of soil (g) divided by the concentration of the chemical in water (mg/ml). Chemicals with high K_d values ($>10,000$) will have a high tendency to adsorb to soil, while those with low values will tend to dissolve in water.

Pollutants may also undergo transformation or be degraded. A transformation is a change in the molecular structure of the pollutant. This includes rearrangement of the molecules, and the addition or loss of certain chemical groups. Degradation, on the other hand, is the breakdown of the pollutant either through the loss of certain chemical groups or the fragmentation of the pollutant. Biodegradation is the biological breakdown of chemicals by microbes. Some of the processes involved in transformation and degradation include oxidation, hydrolysis and photolysis. Oxidation often, but not always, involves the addition of oxygen to a chemical. Hydrolysis is the fragmentation of a chemical through the action of water. This often results in fragments that contain additional hydrogen or oxygen atoms. Photolysis, on the other hand, occurs when a chemical absorbs sunlight and breaks apart into fragments known as photo-degradation products. The prevailing environmental conditions like temperature and the presence of water, oxygen and other pollutants may influence these processes. Some chemicals may resist any changes in structure through transformation processes or degradation. These chemicals are usually described as being persistent. An example of such a group of chemicals is the polychlorinated biphenyls (PCBs).

Exposure pathways and routes

The physical course a pollutant takes from the source of an agent to the organism exposed is often referred to as an *exposure pathway*. The way a chemical, physical or biological agent enters an organism is referred to as an *exposure route*. The three major exposure routes to humans are:

- Inhalation
- Ingestion
- Dermal contact

Other important exposure routes are placental exposure of the foetus, exposure to noise via the ears, and exposure to UV-radiation via the eyes.

The relationships between environmental and exposure media, and exposure pathways and exposure routes are given in Figure 6 (p. 22).

Dose

The amount of a pollutant that may enter the body is usually only part of the exposure, and is referred to as the dose (Figure 4, p. 17). The *absorbed dose* (or internal dose) is the amount of an agent that passes into a tissue or organ over a time interval, for example the concentration of a solvent in blood during, or shortly after, a work-shift. The absorbed dose can also be the amount of an agent accumulated in one or several body compartments. For example, the concentration of polychlorinated biphenyls (PCBs) in blood is proportional to the amount accumulated in the main sites of deposition, mainly fatty tissue. The *target organ dose* is the integrated concentration of the agent in the target organ, that is the organ where the particular agent may cause an adverse effect, over a time interval. The *biologically effective dose* is the integrated quantity after subtraction of the non-contributing fraction of the dose, for example the biotransformed proportion of a substance that may cause an effect (Box 4).

Relationship between environmental concentration, exposure, absorbed dose, target organ dose and biologically effective dose: Lead as an example.

High concentrations of lead in soil are recorded in the vicinity of lead emitting industries such as smelters. That is not an exposure until the lead-contaminated soil in some way reaches the human body. This may indeed happen if soil is consumed via hand-to-mouth behaviour or so called pica (eating of substances other than food) which is not uncommon among young children. Lead in soil may also be taken up by edible plants that are consumed. Soil may contaminate food with lead-containing particles that are not washed off before consumption. The lead absorbed in the gastrointestinal tract becomes the absorbed dose. Lead is to a great extent accumulated in bone but the main target organ in young children is the central nervous system (CNS). Thus, the amount of lead in the CNS is the target organ dose, and the fraction of lead that gives rise to neurobehavioural effects in children is the biologically effective dose.

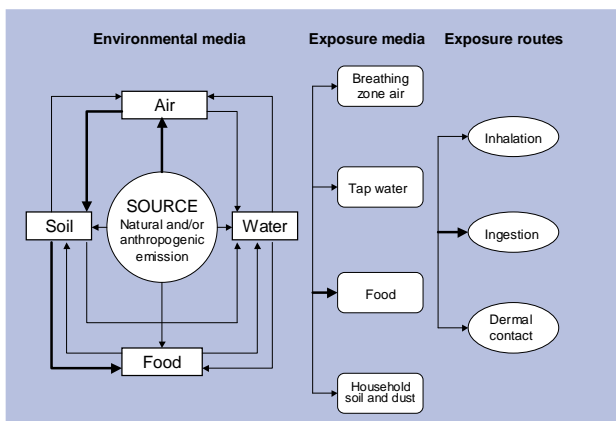


Figure 6. The relationships of environmental and exposure media, and exposure pathways and routes. Bold arrows indicate one example of an exposure pathway (adapted from McKone and Daniels, 1991).

Toxicokinetics

Toxicokinetics describe the processes by which a potentially harmful substance is distributed, metabolised, and excreted, and the fraction that reaches the target tissue. Toxicity is demonstrated in one or several organs. For example, mixtures of chemicals, such as cigarette smoke, affect several organs. After entering the body via the lungs, skin or gastrointestinal tract, the substance is transported to the site of action/target organ. The agent is usually dissolved and transported in blood. The agent may reach the target organ in its active form or it may be activated there. In many cases, the agent is metabolically activated in the liver. The active form binds to cellular macromolecules or is eliminated by detoxification processes, and is excreted in urine, faeces, bile or sweat. The excretion of the agent itself or of a detoxification product, for example in urine, makes it possible to measure or estimate the exposure or dose (Chapter 5, p. 87).

The relationship between exposure or dose and health effects

In Sir Bradford Hill's classical guidelines for determining causation of diseases, one criterion is the 'biological gradient', i.e. the dose-response relationship (Hill, 1965). Exposure assessment is critical in establishing causality. When exposure and dose increase, any adverse effect will usually become more pronounced and a larger number of individuals may be affected. The relationship between exposure and effect is expressed as an *exposure-effect relationship* and the relationship between dose and type or severity of effect is expressed as a *dose-effect relationship* (Figure 7). The relationship between exposure and response is expressed as the *exposure-response relationship* and the relationship between the dose and the proportion of the exposed population that is affected is known as the *dose-response relationship* (Figure 8, p. 24). These concepts are crucial when differentiating between variations in type and degree of effect, and numbers of individuals with defined effects. It should be noted that the terminology used in publications does not always follow this important conceptual distinction.

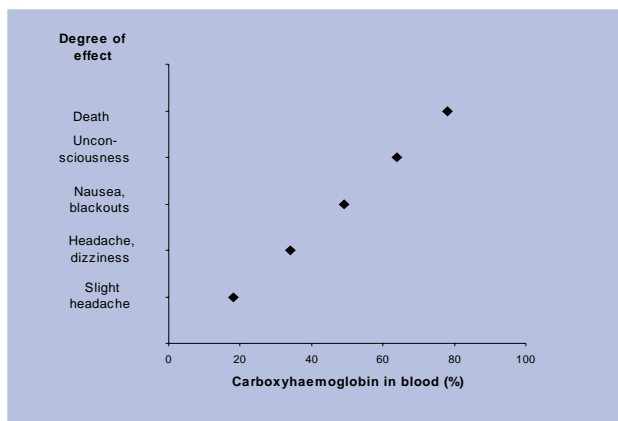


Figure 7. An example of a dose-effect relationship, as the dose increases so does the degree of effect, from slight headache to death (Beaglehole et al, 1993).

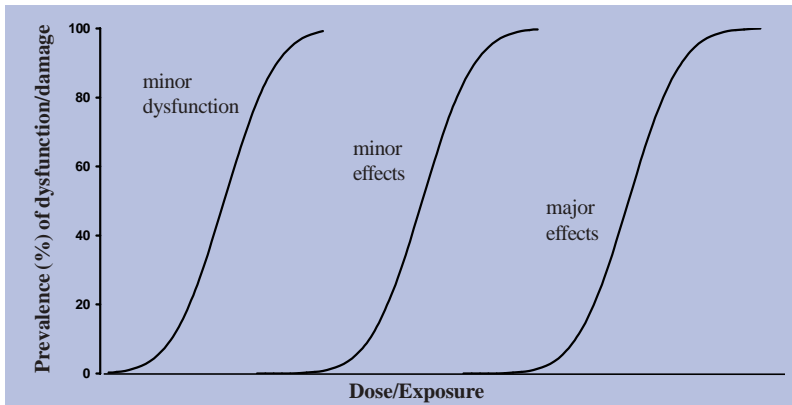


Figure 8. Relationships between dose or exposure and prevalence in percent (response) of individuals, as the dose or exposure increases, so too does the prevalence of individuals experiencing minor dysfunction, minor effects and major effects (response), from a few to almost 100 percent (Elinder et al, 1994).

The scope of human exposure assessment

The aim of human exposure assessment is to identify and quantify past, present and future exposures to chemical, physical, and biological agents that may cause health effects.

Human exposure assessment comprises all the methods available to describe, estimate and determine, qualitatively and quantitatively, the agents' contact with, and entry into, the body. Exposure assessment includes:

- Identification and evaluation of sources of hazardous agents (type, amount released, geographic location)
- Determination of concentrations of agents in environmental media such as air, water, food and soil
- Identification of (major) pathways and routes of exposure
- Determination of intensity, duration and frequency of exposure
- Determination of dose resulting from exposure

- Estimation of number of persons exposed
- Identification of high-risk groups (highly exposed or more susceptible to effects)

For prevention of disease it is essential to know who are exposed, what the exposure sources and levels are, which the health effects are, the subgroups of the population with the highest risk, and the proportion of the population affected. Using this information, measures to reduce exposure and effects can be taken. Human exposure assessment is a complex process, involving many different specialists, such as industrial hygienists, chemists, environmental health physicians and toxicologists.

Key considerations of human exposure assessment

Time and location

Time and location play important roles in human exposure assessment in several ways. Individuals are exposed intermittently throughout a whole lifetime, over time periods of various lengths and of various intensities, depending on what they do and where they spend their time.

Exposure duration and frequency

The duration and the frequency of exposure are both important determinants of total exposure. The minimum duration of exposure causing a disease is often not known. Therefore, it can be important to evaluate exposure over both long and short periods. When health effects from long-term exposure (months, years) are to be evaluated, exposure and dose are usually integrated over the time period of interest. For shorter periods, such as minutes, hours, or days, exposure is usually averaged over the specific time period. The integrated (cumulative) exposure is defined as the area under the curve, determined by exposure concentration and time as illustrated in Figure 9 (p. 26). Cumulative exposure is often used as the exposure index in epidemiological studies, but it may not give a complete picture of the exposure potentially associated with a health outcome. For example, a study of the association between lung cancer and smoking have suggested that lung cancer risk increases with the square of smoking intensity but with the

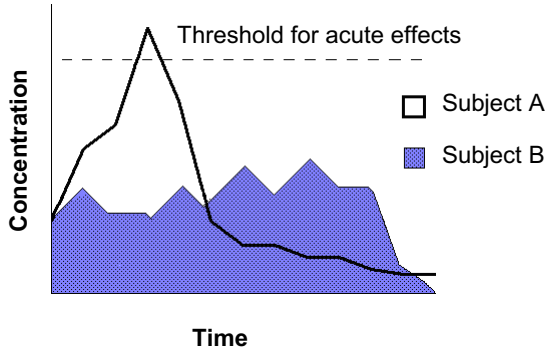


Figure 9. Two individuals experiencing different exposure patterns but the same cumulative dose. During the time period shown subject A encountered considerably higher concentration of the pollutant than subject B, but the cumulative exposure (area under the curve) was the same for both individuals.

fourth or fifth power of smoking duration (Doll and Peto, 1978). Thus, smoking two packs of cigarettes a day for 10 years would not confer the same risk as smoking one pack a day for 20 years, the latter is worse.

If high (peak) exposures in a short time interval cause more harm than an equivalent amount over a protracted period, an index of peak exposures may be useful. For example Enterline (1976) noticed that intermittent exposures to asbestos carried a higher risk than continuous exposures when average exposures were similar. Peak exposures may also cause adverse effects that may be distinct from those of cumulative exposure. Intensity, frequency and duration should be considered in the definition of peaks.

Time between exposure and effects

The time between initial exposure and the occurrence of a health effect can vary from instantly to decades depending on the agent and the type of effect. This is important to know in order to assess exposure for a relevant period of time in relation to the expected effects. For hazardous agents that cause acute effects more or less immediately after exposure starts, the current level of exposure should be measured. An example is carbon monoxide (CO) causing predominantly acute cardiovascular effects due to decreased binding and transport of oxygen in the blood. However, other environmental agents, for example cadmium and lead, can cause health effects after long-term exposure at relatively low levels. They accumulate in the body because of their low rate of excretion (i.e. long biological half-time), and adverse health effects may occur when the concentration has reached a critical level. For carcinogenic agents, the time between exposure and the appearance of a tumour is often in the order of decades, which often makes it necessary to estimate exposure retrospectively, since prospective studies would take too long to complete.

Time-activity patterns and exposure settings

Concentrations of potentially harmful agents differ in relation to time of the day, week, or season, etc., and between different settings. Information on how people use their time, and where they spend it, may influence exposure considerably. Human behaviour and use of time is referred to as the *time-activity pattern* of an individual or a population.

People are moving between various exposure settings with different concentrations of hazardous agents. An exposure setting may be referred to as a microenvironment. A *microenvironment* is a well-defined surrounding such as the workplace, home, vehicle, kitchen, store, restaurant, etc., that can be treated as homogeneous (or well-characterised) with regard to the concentration of a hazardous agent (Duan, 1982). Exposure assessment can be based on measurements of hazardous agents in typical (or all) microenvironments where people spend time, and of the amount of time spent there, i.e. concentration x time for each microenvironment (Box 13, p. 97).

Knowledge of the type of activities performed can assist in identifying sources of exposure, activities contributing significantly to exposure, and in investigating relationships between exposure and health effects (Box 5, p.28).



Time activity data

Time-activity data in combination with microenvironmental concentration measurements or personal measurements can be used to identify sources of exposure and activities that contribute significantly to exposure. For example, measurements of personal exposure to nitrogen dioxide (NO_2) were carried out among children in a community of Sweden where high ambient levels of NO_2 had been measured repeatedly at the outdoor fixed monitoring station in the centre of an urban area. However, it became evident from diaries kept by the children that the most significant source of NO_2 exposure was indoor ice-skating arenas. Children visiting indoor ice-skating arenas showed extremely high exposures (Figure 10). It was concluded that the source of NO_2 was the iceresurfacing machine.

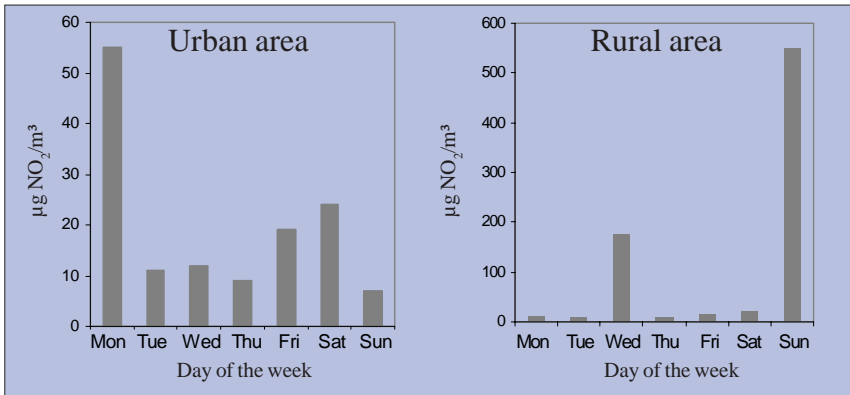


Figure 10. Example of day-to-day variations of NO_2 exposure ($\mu\text{g}/\text{m}^3$) in relation to activities for two children: one living in an urban area (left) and one living in a rural area (right). Notice the ten-fold difference on the y-axis. *Left:* On Monday this child went skating for 2 h in the indoor ice-skating arena. Saturday she spent 3 h in the downtown area, indoors (2 h) and outdoors (1 h). Sunday was spent at home. *Right:* Wednesday (1.5 h) and Sunday (2 h) were spent in the indoor ice-skating arena by this boy (data from Berglund et al, 1994b).

Additional factors modifying exposure and dose

Additional factors influencing the exposure and dose, and which have to be considered in human exposure assessment, include personal habits and preferences of the individual, often referred to as life-style factors, as well as socio-economic and cultural factors, nutritional status, and level of physical activity.

In epidemiological studies it is very important to adequately deal with potential confounders and effect modifiers. A variable associated with the outcome of interest as well as with the exposure under study is a *confounder*, in other words it may distort the associations under investigation (Box 6). A variable is considered to be an *effect modifier* if the association between exposure and the investigated outcome are not the same for different levels of this effect modifier. Confounders and effect modifiers should be measured and quantified in a similar way to the exposure of prime interest.

Life-style factors

Life-style factors such as food choice and smoking habits will influence the exposure and dose. For example, individuals habitually eating a diet rich in shell-fish had a much higher intake of cadmium than individuals eating a fibre rich diet (vegetarian diet) or a mixed diet (Figure 11, p. 30). However, their blood cadmium concentrations were not significantly different, indicating differences in the gastro-intestinal absorption of cadmium depending on nutritional and dietary factors.

Some individuals consume much more drinking-water and beverages than others. Living in hot climates makes it necessary to drink a lot of water. The risk of excessive exposure to fluoride, which may cause osteofluorosis, is therefore higher, for example, in India than in Scandinavia even though the fluoride concentration

Example of a confounder that should be considered and quantified

Passive smoking or environmental tobacco smoke (ETS) is a risk factor for respiratory symptoms. Indoor air pollution from the use of gas for cooking is also a risk factor for respiratory symptoms. If the association between asthma symptoms in children and indoor air pollution from gas stoves is to be assessed, exposure from passive smoking must also be measured. If those cooking with gas have different ETS exposure patterns than those not cooking with gas, the association with asthma symptoms may be confounded.

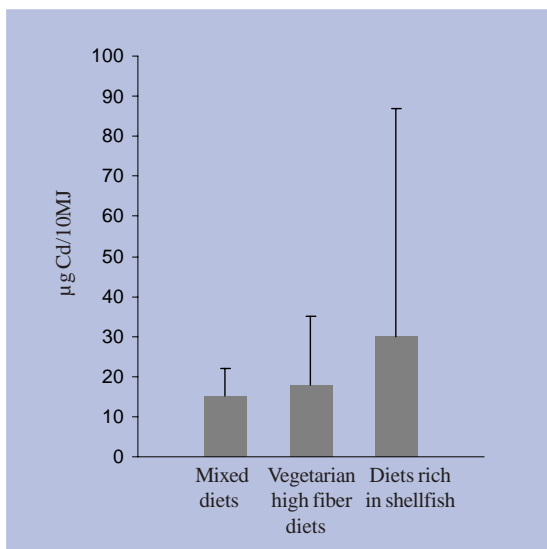


Figure 11. Intake of cadmium via different types of diets (medians and 95-percentiles, $\mu\text{g Cd}/10\text{MJ}$; data from Berglund et al, 1994a; Vahter et al, 1996).

in drinking-water is similar. Some people may consume only bottled water. Therefore, it is important to investigate the actual water intake in a population when performing a study of the exposure via drinking-water, instead of using a default value of, for example, 2 litres/day for an adult.

Socio-economic and nutritional status

Socio-economic and nutritional status may affect exposure and dose. Low socio-economic status (measured by income, education, housing or occupation) appears to increase both the environmental exposure and the susceptibility, for example due to poor nutrition. However in relatively high socio-economic classes, low nutritional status such as iron deficiency in women is also common. For example, in Swedish women of childbearing age (including all social classes), it was shown that 10-40 % of the women had depleted body iron stores (Hallberg et al, 1993). Iron deficiency has been shown to increase the absorption of cadmium in the gastrointestinal tract, leading to increased blood cadmium concentrations and increased body burden of cadmium (Berglund et al, 1994a; Åkesson et al, 2002).



Deteriorating leaded paint in old housing is a significant source of lead exposure, especially in young children, due to their hand-to mouth behaviour. Lead paint exposure is particularly common in deprived areas with a large proportion of old houses. Lead concentrations in household dust and garden soil may be very high, leading to high exposures.

Polychlorinated biphenyls (PCBs) - synthetic hydrocarbon compounds once used as insulating materials and capacitors - are among the most persistent and ubiquitous environmental contaminants. Environmental emissions of these compounds have given rise to a marked accumulation in the food chain, including certain species of edible fatty fish. If the contaminated fish is consumed, this may cause significant human exposure. *In utero* exposure to PCBs has been linked to adverse effects on the development of children (Box 7). Interestingly, and in contrast to environmental lead exposure, exposure to PCBs in the study by Jacobson and Jacobson (1996) was not related to poverty or deprived social circumstances.

 **BOX 7**

Intake of contaminated fish gave rise to developmental effects in children.

Jacobson and Jacobson (1996) have studied women and their children who consumed fish from the contaminated Lake Michigan. PCBs and a number of other pollutants were determined in maternal and umbilical cord blood, breast milk, and in blood samples from the children at ages 4 and 11. The cognitive function of the children was tested at age 11. There were significant negative associations with perinatal exposure to PCBs and several of the cognitive function tests. Various confounders such as educational level of the mother were considered, but the overall finding that early PCB exposure may affect the intellectual development remained.

Physical activity

Physical activity has effects on uptake, metabolism and distribution of agents inhaled. For example, someone who is exercising heavily may inhale more than ten times as much air per minute as a person at rest. Differences in individual ventilation patterns, for example mouth and nose breathing, also influence deposition and absorption of inhaled substances. Åstrand and co-workers (1983) have examined the effects of exercise on the uptake, metabolism, and distribution of solvents. They observed that even mild exercise might increase the rate of uptake and change the pattern of blood flow through the tissues. Because of these changes, the relationship between target tissue concentration and exposure level may also change dramatically.

Figure 12 shows how the time course of ethylene oxide (EtO) concentrations varied in the three main tissue groups as a function of different levels of light exercise: 10 watts sedentary work versus 50 watts light work. The increased respiration and cardiac rates associated with 50 watts of work resulted in twice the levels of EtO in the tissues as those associated with 10 watts of work. The skin/muscle group displayed the largest increase because of the increased blood flow in these tissues. Thus, two exposure situations with identical air concentrations of EtO resulted in a more than twofold difference in the individual dose.

Exposure distributions and high-risk groups

There are large variations in exposure between and also within individuals due to variation in behaviour, activity patterns and other factors modifying exposure and dose. Thus, not everybody in the general population is equally exposed and not everybody in the general population is at the same risk, given some level of exposure.

Identification of high-risk subgroups is important from a public health perspective (Figure 13). Certain individuals may be at higher risk because they are more exposed than the average individual; that is, they are at the high end of an exposure distribution. For example, vegetarians are potentially more exposed to agricultural pesticides and cadmium than the general population, because of their higher intake of vegetables, fruit, and rice. Other individuals may be at higher risk because they are more susceptible to exposure; thus, they may develop health effects at lower exposures than the average person. Potential causes of

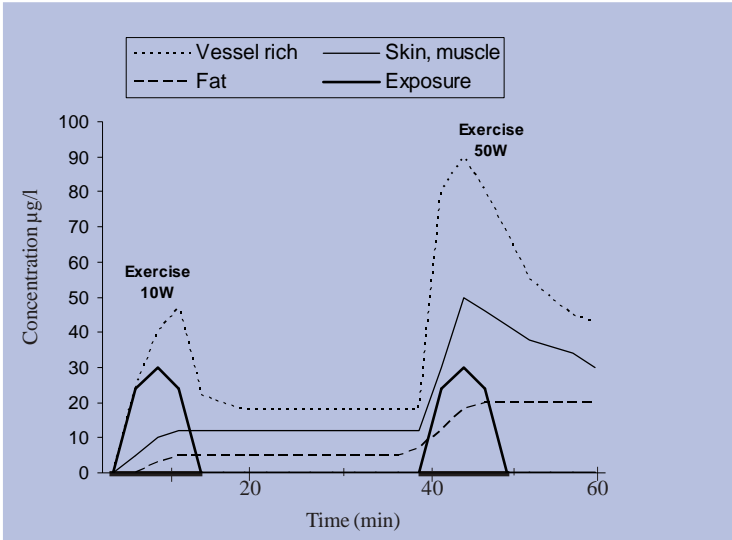


Figure 12. Physiological model estimated tissue concentrations of ethylene oxide in the three major tissue groups for two identical periods of inhalation exposure but different levels of exercise (adapted from Åstrand et al, 1983).

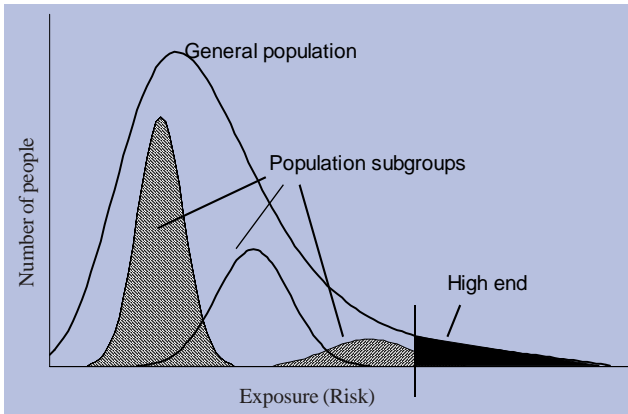


Figure 13. Hypothetical exposure distributions illustrating the relationship between the general population and population subgroups (adapted from Sexton et al, 1995).

enhanced susceptibility are genetic predisposition, age, gender, pre-existing disease (for example, asthma, diabetes), inadequate nutrition and stress. For example, foetuses and young children are more susceptible to lead because of their immature blood-brain barrier and central nervous system.

After reading this chapter you will:

- Be aware of the principal applications of human exposure assessment
- Be able to identify the requirements of exposure assessment in environmental epidemiology, risk assessment/management and documentation of status and trend
- Understand the importance of appropriate exposure information in health prevention and promotion

Exposure assessment data are used mainly in four interrelated disciplines, that is epidemiology, risk assessment, risk management and status and trend analysis (Sexton et al, 1992).

Epidemiological studies examine the link between human exposures and health outcomes. *Risk assessment* estimates the likelihood, magnitude, and uncertainty of health risks associated with exposures. *Risk management* deals with the level of health risks in the society, and what to do about them. *Status and trend studies* evaluate historical patterns, current status and possible future changes in human exposures.

Occupational and environmental epidemiology

Epidemiology is the study of the occurrence of disease and its determinants in human populations. For more than a century, epidemiological studies have played an important part in investigations of infectious disease. Today, epidemiological methods are increasingly used to study effects of chemical and physical environmental agents.

Epidemiological studies often concern chronic diseases (such as cancer) with long latency periods, for which the time between actual exposure and onset of disease may be very long, sometimes in the order of decades. Thus, previous rather than current exposure levels may be associated with the disease. To study the associations between previous exposure and current disease is thus one of the major challenges in modern epidemiology.

Retrospective or historic exposure assessment is very important in many epidemiological studies. Sometimes retrospective exposure assessment is relatively easy. Lead, for example, accumulates in bone and teeth, and analysis of lead in these materials may thus provide a good estimate of the accumulated dose (Chapter 5, p. 93). In most situations it is, however, much more difficult to assess previous exposures.

Indices of historical exposures may include for instance duration of employment in a plant (occupational exposure) or period of residency in a polluted area (environmental exposure). The most important factors for determination of historical exposures are duration (time) and intensity (concentrations).

Occupational or environmental epidemiological studies examine associations between exposures to occupational or environmental agents and associated diseases. Occupational exposures have been very high in many industries in the Western world, but have continuously decreased during recent decades. In developing countries in the beginning of industrialisation, occupational exposure may still be high. In the developed countries, environmental exposures are often low and not specific, but in many other countries in the world environmental exposures are still relatively high.

The objective of an epidemiological study is to assess whether an exposure has an effect on health, by comparing the health effects of exposed to unexposed persons (Baker et al, 1999).

The following table (Table 2) illustrates different exposure assessment related problems encountered in occupational and environmental epidemiological studies.

Table 2. Differences between occupational and environmental exposure assessment.

Issue	Occupational	Environmental
Exposure prevalence	Confined to specific occupational settings	Often commonly occurring, but not specific
Exposure range	Wide range of exposures within an industry is relatively common	Limited range of exposures, that is “high exposure” is not very different from “low exposure”
Exposure characteristics	Single (or a few) exposure common	Often multiple exposures (complex mixtures) but usually only a single exposure included in study
Individual exposure data	Often lacking, but data from representative work places may be good surrogates	Often lacking, group or community based data may be less good surrogates
Public health importance	Limited	Large populations often exposed, and therefore the impact of low excess risks may be important

As study design and methods are essential for sound environmental epidemiology, we refer to the abundant epidemiological literature. The following sections give only a brief overview of the most important study designs. The appropriate strategies to deal with the above mentioned challenges of environmental epidemiology depend on the chosen study design, the research question and the methods.

Exposure assessment in various types of epidemiological studies

Depending on the study design and purpose of the epidemiological study, various types of exposure data are needed.

Cohort studies

Cohort studies follow health events occurring in exposed subjects over time. One example of a cohort study is given in Chapter 9 (The Bhopal disaster).

Prospective cohort studies require basic documentation of present exposure. Since most exposures vary over time, it may be necessary to measure exposure repeatedly during the follow-up period. For example, in the cohort study of male British doctors initiated in 1951 by Doll and Hill, doctors were re-surveyed regarding their smoking habits in 1957, 1966 and 1972 (Doll and Peto, 1978). Over the study period the prevalence of current smoking in the cohort decreased markedly. Disease incidence and mortality pattern could be extensively studied as a function of individual smoking histories.

Retrospective cohort studies have been commonly used in the study of work environment related diseases. Historical occupational exposure data may be obtained from many different sources. The initial step is usually to identify the potentially toxic agents. Sometimes this is a relatively easy task, for example when the concern is exposure to agents with known toxic properties, such as asbestos or arsenic.

In other cases both type of exposures and their concentrations may vary over time. Commonly, it is not only a single agent which is of interest for the outcome under study. Instead, complex mixtures of compounds may be responsible for the causation of disease. Such mixtures are, however, rarely studied, partly due to design difficulties. In relatively few studies has the interaction been analysed between two toxic agents, for example between arsenic and smoking, or asbestos and smoking, as risk factors for lung cancer.

It is also important to identify confounding exposures to be able to compute potential exposure response relationships in an accurate way.

Records of employment are commonly used in occupational epidemiology, sometimes supplemented by measurements of specific substances in the work environment. A rarely used alternative to records is the reconstruction of previous work place environments in which actual measurements can be performed.

One of the most commonly used retrospective exposure estimates in occupational epidemiological studies is duration of employment, which does not take into account levels of concentration of the agents under study. An exposure profile over time for the entire plant adds further information to the exposure assessment. Combining such a profile with the individual worker's employment records yields cumulative exposure values for each worker, but does not take into account air concentration variations within the plant. Nevertheless, this rather crude cumulative exposure estimate may yield strong associations between exposure and disease as shown in the example given in Box 8.

If more detailed information is available with, for example, different exposure concentrations in different plant areas or workshops, the degree of mis-classification of exposure naturally decreases and thus the precision of the study increases. A goal for retrospective exposure assessment is to possibly reach this level of refinement, but the work is very time-consuming and thus expensive. Therefore, rather few studies have been published using such refined exposure estimates.

Cumulative cadmium exposure and prevalence of kidney dysfunction

Cadmium is a heavy metal with a very long biological half-time. The critical organ is the kidney and the first sign of cadmium induced renal damage is a urinary excretion of low molecular weight proteins, such as beta-2-microglobulin, due to decreased reabsorption in the renal tubules. The prevalence of tubular proteinuria was studied in a cohort of 900 nickel-cadmium battery workers in Sweden. A rough estimate of the cadmium concentrations in workroom air over time was used as a surrogate for individual exposure. The cadmium concentration for each time period was linked with the work files and cumulative exposure indices were computed for each worker. Using these rather crude estimates of exposure, it was possible to establish exposure response relationships for cadmium exposure and the prevalence of tubular proteinuria (Table 3; Järup et al, 1988).

Table 3. Exposure-response relationship between cumulative exposure to cadmium in work room air and the prevalence of tubular proteinuria in Swedish nickel cadmium battery workers (Järup et al, 1988).

Cumulative exposure to cadmium in air $\mu\text{g}/\text{m}^3$ year	Cases of tubular proteinuria	Total number of exposed subjects	Prevalence of tubular proteinuria %
<359	3	264	1.1
359 - <1710	7	76	9.2
1710 - <4578	10	43	23.3
4578 - <9458	10	31	32.3
9458 - <15000	5	16	31.2
15000 +	5	10	50.0

Another way of assigning exposures to individual workers is by so-called Job Exposure Matrices (JEMs). A matrix consisting of job titles and relevant exposure levels can be estimated. Often exposure has changed over time and commonly JEMs therefore include several time periods with varying exposure levels. Typically, in the early years of a factory operation the exposures were much higher than in later years, when various control measures had been implemented.

Useful data sources for generating a job-exposure matrix have been suggested and are listed below (Checkoway et al, 1989):

- Industrial hygiene or health physics sampling data
- Process descriptions and flow charts
- Plant production records
- Inspection and accident reports
- Engineering control and protective equipment documentation
- Biological monitoring results

Historical archives containing information on, for example, industrial processes and control measures are useful but rarely found in smaller industries. Even in large industries such records may be hard to obtain. In a few cases, measurements of toxic agents have been made throughout plant operation. Even if historic files exist the task of developing a JEM also includes interviews with, for example, former employees, trade unionists and occupational health physicians.

Case-control studies

A case-control study (or case-referent study) examines the association between exposure and a health effect by comparing individuals who have developed the disease (cases), with individuals who have not (controls or referents), and who are from the same population as the cases (Box 9). In case-control studies, exposure assessment should allow inferences about past exposure, usually a long time before onset of disease. Such studies therefore most often rely on personal interviews, self-administered questionnaires and available records about the study persons and the exposures they may have encountered. Information on present exposure data is sometimes used in case-control studies, but assumes stability of exposure over time. This is rarely the case however and therefore mis-classification of exposure is likely. Asking an individual about present smoking habits alone may thus yield completely wrong information about previous smoking, since the respondent may have quit smoking recently. Another example is the use of current air pollution data to describe retrospective exposure to air pollution. Changes in heating systems and the development of road traffic over time would most likely be considerable, eventually leading to substantial mis-classification of exposure.

The so-called nested case-control design uses a previously existing cohort. For cases of a disease under study and a number of controls within the cohort, additional detailed information of relevant exposures and confounders may be obtained for example through questionnaires sent to cases and controls. Thus, data on exposures and other risk factors will be required only for the cases and their controls, and thereby costs can be cut.

A case-control study of lung cancer in Stockholm

In a case-control study of lung cancer in Stockholm, exposure to air pollution was assessed through a postal questionnaire combined with dispersion modelling of relevant air pollutants (Nyberg et al, 2000). Cases and controls (or their next of kin, when the respondent was deceased) were asked questions on their previous and current residential addresses. This information was combined with information on air pollution data derived from the dispersion modelling to get individual cumulative air pollution estimates. Questions were also asked about other potential risk factors for lung cancer, smoking being the most important. Exposure to environmental tobacco smoke was assessed, as well as certain dietary habits, in particular consumption of vegetables with potentially protective properties. The study showed an increased risk for lung cancer associated with exposure to road traffic generated air pollutants.

Cross-sectional studies

In cross-sectional studies, data on exposure and health outcome are collected at the same time (Box 10). The association between exposure and prevalence of the health outcome is studied. These studies may use the current exposure situation and sometimes, also past exposure. In the latter case, the same methods as used in retrospective studies may be applied. Direct measurements of current exposure are often convenient to perform and, in fact, are an advantage of the cross-

BOX 10



The Cadmibel study

Studies on kidney damage (tubular proteinuria) after (long-term) cadmium exposure have mostly been cross-sectional. A good example of a large cross-sectional study that has had great impact on consequent research as well as on public health action is the so-called Cadmibel study (Buchet et al, 1990). In this study, 1699 subjects aged 20-80 years were studied as a random sample of four areas of Belgium with varying degrees of cadmium pollution. After standardisation for several possible confounding factors, several urinary markers of tubular dysfunction were significantly associated with the urinary excretion of cadmium (a marker of cadmium body burden). The results suggested that subclinical changes in tubular function might occur in the general population above a threshold of urinary cadmium as low as 2 µg/24h.

sectional study design. A major disadvantage of concurrent assessment of exposure and health is the inability to establish the temporal sequence of exposure and health outcome. This is particularly true for situations where a disease may cause a change in the exposure pattern, for example asthmatics tend to give up smoking due to the disease.

Ecological studies

The collection of individual exposure data is expensive. Ecological studies make use of often easily available aggregate data such as average exposure or proportion of population exposed, for example the prevalence of smoking in a county (“exposure”), and the mortality rates (“outcome”) for the same population. The statistical correlation of aggregate data may strongly differ from the true exposure-effect association. Due to the lack of individual data, control of confounding is not possible and, in contrast to studies on the individual level, it cannot be anticipated whether ecological correlations are stronger, weaker, or similar to the individual level associations. For that reason, truly ecological studies are inadequate sources for etiological inference. It must be emphasised that for example cohort and cross-sectional studies, although collecting individual data, may use “aggregate” exposure data rather than individually measured exposures. Examples

may be job titles in occupational epidemiology or the average level of ambient air pollution in the region of residence. Such a design may be termed “semi-individual” (Künzli and Tager, 1997).

However, ecological studies may be useful for hypothesis generation. Routinely collected data on exposures (such as air pollution levels) and health outcomes (such as mortality, cancer incidence and hospital admissions) may be used for ecological analysis. The results from such analysis may indicate if further more detailed epidemiological analysis is warranted. An example of how routinely collected data have been used successfully to assess potential health risks associated with environmental exposures is the Small Area Health Statistics Unit (SAHSU) in the United Kingdom. SAHSU was established in 1987 to respond to environmental health risks, following the alleged association between exposure to radiation from the Sellafield nuclear power plant and childhood leukaemia. To be able to make a first assessment quickly, which is often essential, SAHSU has developed a technique, using Geographic Information Systems (Chapter 5, p. 98), which computes relative risks around a potential source of environmental exposure (Aylin et al, 1999). These initial analyses can be performed in a few hours, and may give an indication of potential health risks, enabling further steps to be taken without delay.

Time series studies

Time-series analyses have been commonly applied to studies of air pollution and acute health effects. A well-known example of a time-series study is the London fog episode of 1952 (Box 1, p. 3). Time-series studies analyse exposures and associated short-term outcomes repeatedly in the same group of people over time. An advantage of this design is that individual life-style factors (for example diet and smoking) which may be confounders do not influence the analyses since the study individuals are their own controls. However, time dependent factors such as temperature and other meteorological factors may confound associations in time-series studies, and must therefore be controlled for. Several recent large studies of ambient air pollution and acute health effects have found an almost linear association between increases in the air pollution levels and increase in the daily number of deaths on the same day or over the next few days. Although the relative risks are low, for particles typically in the order of a 0.5-1 % (RR=1.005-1.01) increment for a 10 $\mu\text{g}/\text{m}^3$ change in PM_{10} , statistically significant and consistent results have been observed in cities around the world (Dockery and Pope, 1994). Although these studies show that mortality (and hospital admissions)

increase if the air pollution levels increase, the time-series design cannot estimate the prematurity of these events. Air pollution episodes may thus “harvest” death among those so severely ill that they would have died within days even without any increased air pollution levels. To establish the full impact of air pollution on life expectancy, it is necessary to perform cohort studies with long-term follow-up (Dockery et al, 1993).

Risk assessment and risk management

Exposure assessment and exposure control are important tools in the processes of risk assessment and risk management. Risk assessment gives a quantitative estimate of the risk of a specific health effect based on available exposure data, and risk management uses this information to set priorities, improve decision-making, and produce more efficient risk (exposure) reduction strategies.

Scientific results from health effect studies associated with environmental exposures have frequently been interpreted differently by scientists and lay persons. It is thus very important that scientists produce not only scientific measures of such health risks but also make efforts to disseminate the results so that lay persons will understand the significance of the findings. This is referred to as *risk communication* and is not always an easy task. It may be wise to consult experts from the social science field to assist in the dissemination strategy. A number of social science research methods have been used to investigate risk perceptions, risk communication and public participation.

Risk assessment

Risk assessment is a formal process used to estimate the likelihood and magnitude of adverse health effects caused by a hazardous agent in humans. The assessments of risks to human health involves the scientific examination and evaluation of information in three areas:

- The hazardous nature of agents in the environment
- The degree of human exposure to such agents
- The impact of such exposure on people’s health

A basic framework for the process of risk assessment for human health effects has evolved through national and international consensus and is now well accepted. Risk assessment process can be divided into four parts (NRC, 1983; Risk Assessment and Toxicology Steering Committee, 1999):

- Hazard identification
- Hazard characterisation (dose-effect and dose-response assessment)
- Exposure assessment
- Risk characterisation

Hazard identification

Hazard identification is based on data from human and animal studies, in vitro test systems, structure-activity relationships and other relevant data to determine whether exposure to an agent can cause adverse health effects in humans (qualitative estimate). For example, can exposure to benzene cause leukaemia in humans? The amount of toxicity data available for risk assessments varies considerably depending on the type of substance and the intended use. For risk assessments of substances that are specifically regulated, such as drugs, pesticides, and food additives, there is usually a complete set of toxicity data available. However, for pollutants formed in the environment, or unintentionally produced and released to the environment, the available data may be scarce.

Hazard characterisation

Hazard characterisation is the quantitative evaluation of the adverse effects observed, usually by dose-response assessment, the evaluation of mechanisms of action, and species differences in response. If available, environmental epidemiology studies may provide the most relevant dose-response estimates for environmental exposures, established under “real life” conditions. However, with few exceptions, there are no empirical human data concerning relationships between dose and effect or response at low exposure levels. High exposure situations, such as the chemical accident in Bhopal (described in Chapter 9) or poisonings, such as the mercury poisoning of the general populations in Minamata and Iraq (Box 1, p. 3), and experimental animal data are often the only data available. Therefore, extrapolations from high to low doses and from animals to humans are necessary, which make the estimates highly uncertain. Mathematical models are often used to predict the effects at low-dose levels. Still, regulatory authorities need those estimates in order to establish, for example, guideline values for drinking-water quality and threshold limit values for work-room air.

Exposure assessment

Exposure assessment identifies and defines the exposure that occurs, or is anticipated to occur, in human populations. Quantitative measures of exposure are essential to improve validity and to reduce uncertainty in risk assessment and management. However, all types of exposure data have to be considered in the processes if there is a lack of quantitative data. Ideally, exposure data should include evaluation of sources of pollutants (pollutant type, amount released, geographic location), pollutant concentrations in air, water, soil and food, exposure routes, intensity, duration and frequency, and resulting doses (absorbed doses, target doses, concentrations of biomarkers). The exposure level and the number of persons exposed should be estimated for different groups of the general population, in particular susceptible groups and highly exposed groups. Furthermore, the relative contributions of all important sources and exposure pathways to the associated target dose should be determined. If all those data were available, risk assessment and management would be a relatively easy task. However, this is never the case. Instead, exposure assessment often have to be modelled based on environmental concentrations of a pollutant in a specific environmental media (for example the concentration of a drinking-water pollutant) and assumptions about the average intake of that medium in a population (for example a default value for daily intake of water. In risk assessment, conservative assumptions about exposure are typically used in order not to underestimate the risk (Table 4). This will of course lead to an overestimation of the risk for a number of people, and in some cases to an underestimation of the risk. More detailed exposure information would in most cases lead to a more effective risk assessment.

Table 4. Examples of default values, which can be used in exposure assessment.

Drinking-water	Adults	1-2 litres/day
	Children \leq 1 year	About 1 litre/day
Air inhaled	Adults	10-20 m ³ /day
Soil intake	Children	100 mg/day
Food	Adults	25 g/kg body weight and day

Risk characterisation

Risk characterisation is the summary of the entire risk assessment process. The summary includes an estimation of the probability of an adverse effect in a human population based on the hazard identification, the dose-response and the exposure information. For example, how many cases of leukaemia are caused by a defined exposure to benzene in a specific population? The uncertainty of the risk estimate and the severity of the effect should be taken into account.

Risk management

The risk estimate and a summary of the relevant biological information, the assumptions used and their limitations, as well as a discussion of the variability and uncertainty in the risk assessment, are used in risk management decisions. Risk management involves three basic types of decisions:

- Determination of “unacceptable” risks
- Selection of the most cost-effective method for prevention or risk reduction
- Evaluation of the success of exposure and risk reduction efforts (exposure and risk control)

Risk managers often have to decide which health effects are unacceptable, based on crude data. For example, regulatory action may have to be taken based on exposure data long before epidemiologists have quantified the health impacts. As new information becomes available, risk management decisions should be re-evaluated. In the absence of good exposure

Determination of a threshold value or NOEL, and its use in calculating an acceptable daily intake, ADI

A threshold value, or the so-called No-Observed-Effect-Level (NOEL), can be determined in experimental animal studies. Groups of animals are given different doses of the substance to be tested, for example, a food additive. A number of parameters are measured, according to the toxicological testing guidelines for food additives, in order to detect any adverse effect to which the substance administered could have given rise. The highest dose tested without effects in the animal experiments (NOEL) is divided by an (arbitrary) uncertainty factor. The uncertainty factor approach has often been used to calculate acceptable (or tolerable) daily intakes (ADIs or TDIs):

$ADI = NOEL / \text{Uncertainty factor}$

Although arbitrary, the uncertainty factor is intended to compensate for the uncertainty and variability inherent in the NOEL value. Often an uncertainty factor of 100 is used, allowing for a 10-fold difference in sensitivity between animals and humans, and a 10-fold difference in human variability.

information, policy makers may make erroneous assumptions about risks, which may result in overly costly control measures. For political reasons, despite an increasing knowledge about potentially harmful exposures, preventive action is often slow to materialise. This is especially true in developing countries, where environmental and occupational exposures can exceed national and international guidelines considerably without any preventive action being taken.

Risk managers should understand the quality of the data (validity and uncertainty) before determining its appropriateness in decision making. The basic issues that should be considered are, according to Burke et al (1992):

- Sampling issues
 - Are valid methods used?
 - Is there an adequate number of samples?
 - Is the level of detection appropriate for the risk being investigated?
 - Are the laboratory methods for quality assurance and quality control adequately documented?

- Population issues
 - Can highly exposed subpopulations be identified?
 - Is the exposure of sensitive subpopulations measured?
 - Is the variability of exposure in the population measured?
 - Do the methods provide a representative sample of the population?

- Exposure data issues
 - Are the data relevant geographically?
 - Are the data correct temporally (i.e. current, seasonally appropriate)?
 - Are the relevant pathways of exposure measured?
 - Do the data measure trends in exposure that can be used to evaluate the effectiveness of risk-management efforts?

The severity and costs of the effects on health, the feasibility of reducing the risk, the cost of taking action (including considerations of benefits and alternatives) and the social attitudes towards the risk need to be considered in risk management.

Status and trend evaluation

Evaluation of the current status and the historical trends in environmental exposures is an important component of epidemiology, risk assessment and risk management. Evaluation requires collection of exposure information for a relatively long period of time so that temporal and spatial trends in the data can be identified and understood. Historical exposure data can be invaluable for identifying new or emerging problems, recognising the relative importance of emission sources and exposure pathways, assessing the effectiveness of pollution controls, distinguishing epidemiological research opportunities and predicting future changes in exposures and effects (Sexton et al, 1992).

Important aspects of status and trend studies are:

- Consistency over time, both in sampling and analytical methods, including differences in detection limits of the analytical methods used over time
- Appropriate frequency of sampling to detect possible changes and to cover variations due to time of day, seasonal variation and age-dependant changes
- Representativity of the samples

In facilitating exposure trend analysis, the creation of biological specimen banks has proven very useful. Archived samples may enable trend analysis of new environmental pollutants as they emerge and are recognised as problems, and evaluation of exposure reduction efforts. One example of a trend study is the analyses of pesticides (p, p' - DDT and p, p' - DDE) and polychlorinated biphenyls (PCBs) in archived Swedish human milk samples (Figure 14, p. 50). The positive effect of the prohibition of DDT in Sweden in 1970 is noticed in the decrease of the concentrations in milk. One advantage of analyses of banked samples is that development in analytical techniques, such as increased sensitivity of the methods and decreased analytical detection limits, does not have to be corrected for in the trend analysis. On the other hand it should be realised that reduction and/or degradation of the agent in the sample may take place during storage. For example, reduction of an agent in a sample may take place due to evaporation or binding of the agent to the storage material. Degradation may take place due to high temperature or instability of the agent. Therefore, banking of samples requires specific considerations regarding sampling materials and storage conditions. Furthermore, ethical considerations need to be addressed (Chapter 8, p. 123).

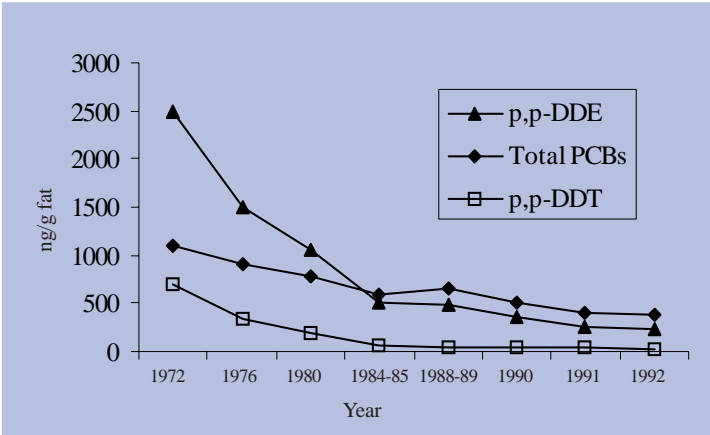


Figure 14. Concentrations of some organochlorine contaminants in human milk 1972-1992 (data from Lundén and Norén, 1998).

After reading this chapter you will:

- Be familiar with basic strategies for assessing exposure, including use of existing data, and direct and indirect approaches
- Recognise the methodological limitations in exposure assessments and their effects on study outcomes
- Recognise the needs for improving the information gaps in the exposure information data base

Different approaches to human exposure assessment

Human exposure assessment may be carried out directly or indirectly (Figure 15, p. 52). *Indirect methods* involve questionnaires and diaries (personal and home characteristics, time-activity patterns and exposure factors), environmental (or area) monitoring, and modelling. Emission inventories and models of the transport and fate of pollutants in the environment may also be used, although they are generally not primarily designed for exposure assessment. *Direct methods* involve personal exposure monitoring and biological monitoring. The choice of method and strategy depends on the purpose of the study and the data quality that is needed to address the questions to be answered. Indirect methods generally provide exposure information at a lower cost than direct approaches. However, indirect methods do not link pollutant concentrations with internal doses as personal and biological monitoring do. This does not mean that personal exposure measurements by default are superior to environmental measurements.

It is often useful to combine two or more methods to gain as much information as possible, and to test the robustness of the results. For example, personal exposure measurements are often combined with information from questionnaires and time-activity diaries, and may also involve measurements of biomarkers.

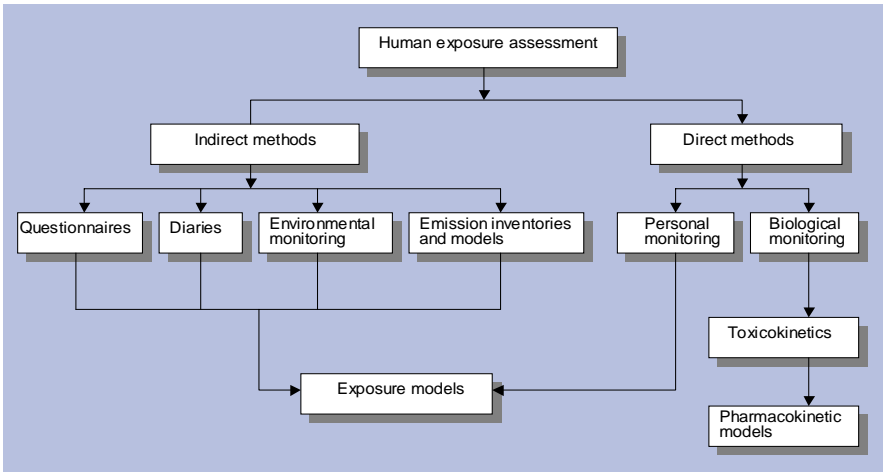


Figure 15. Different approaches to human exposure assessment (adapted from NRC 1991b).

The most important route of exposure may not always be easily ascertained. Therefore, it may be important to consider the potential contact with all media and routes, that is to conduct a *total* or a *multimedia, multipathway exposure assessment study*. For total exposure assessment, data should be gathered for all environmental media and routes of entry, and from personal measurements (Lioy, 1990). These data are useful for determination of the most important sources and routes of exposure, estimation of the intensity and duration of exposure as well as assessment of the relationship with known health effects. Individual exposure data can also be used for validation of human exposure models. Methods of assessing exposure and dose are described in chapter 5.

Planning a human exposure assessment study

The first consideration of a human exposure study should be the purpose and objectives of the study. Hypotheses should be established prior to study start, and the end use of the data should be considered. For example, the study may:

- Examine long-term effects of emission control strategies on the exposure to a contaminant in the general population
- Provide information on exposure magnitude and variance in order to plan and design additional studies
- Compare exposure levels between various groups of a population
- Identify high-risk groups

There may be more than one objective, which is why it is important to choose study parameters that properly address the questions to be answered.

Secondly, the study parameters should be defined. Study parameters include the population to be studied, pollutants to be studied, measurement techniques and the time frame of interest. Several aspects of the contact between people and hazardous substances have to be considered in the planning of an exposure study, and in the following exposure analysis. These have been summarised in Table 5 (p. 54). A study plan, describing *what*, *where*, *when* and *how* data shall be collected, as well as a detailed sampling protocol should be developed.

Furthermore, procedures for quality assurance and quality control should be outlined (Chapter 6, p. 101). Quality data should be reported together with the exposure data to make it possible to compare the results with other studies. Finally, statistical considerations should be addressed (Chapter 7, p. 115); ethical implications have to be considered (Chapter 8, p. 123); necessary approval from ethics committees must be obtained, and the study has to be financed before it is started.

Table 5. Different aspects of the contact between people and pollution that are potentially important when planning a study, and in the following exposure analysis (adapted from Sexton et al. 1995).

Agents	Sources
<ul style="list-style-type: none"> • Biological • Chemical • Physical • Single agent • Multiple agents • Mixtures 	<ul style="list-style-type: none"> • Anthropogenic/Nonanthropogenic • Area/Point • Stationary/Mobile • Indoor/Outdoor
Transport/Carrier media	Examples of exposure pathways
<ul style="list-style-type: none"> • Air • Water • Soil • Dust • Food • Product/Item 	<ul style="list-style-type: none"> • Eating contaminated food • Breathing contaminated air • Touching contaminated surfaces
Exposure concentration	Exposure routes
<ul style="list-style-type: none"> • mg/kg (food) • mg/L (water) • $\mu\text{g}/\text{m}^3$ (air) • $\mu\text{g}/\text{cm}^2$ • % by weight • Fibers/m^3 (air) 	<ul style="list-style-type: none"> • Inhalation • Ingestion • Dermal contact • Multiple routes
Exposure duration	Exposure frequency
<ul style="list-style-type: none"> • Seconds • Minutes • Hours • Days • Weeks • Months • Years • Lifetime 	<ul style="list-style-type: none"> • Continuous • Intermittent • Cyclic • Random • Rare
Exposure settings	Exposed population
<ul style="list-style-type: none"> • Occupational/Nonoccupational • Residential/Nonresidential • Indoors/Outdoors 	<ul style="list-style-type: none"> • General population • Population subgroups • Individuals
Geographic scope	Time frame
<ul style="list-style-type: none"> • Site/Source specific • Local • Regional • Days • National • International • Global 	<ul style="list-style-type: none"> • Past • Present • Future • Trends • Lifetime

Study population

Who should be included in the study?

There are basically three main types of study design to consider when choosing a population to study (Lee et al, 1989). *Comprehensive* studies include all members of the study population; a *survey* (or probability sample study) is based on a randomly selected, representative sample of individuals; *anecdotal* studies consist of a convenient (non-random, non-probability) sample of the population.

Comprehensive studies are typically carried out when the total population is small since the costs would be too high in a large population. A survey, or probability sample study, aims to remove selection bias and is useful for generalising results beyond the persons studied and to the general population. A random sample of the study population should be investigated in order to get exposure distribution data. For information on random sampling strategies, the reader is referred to the specialized literature (Kalton 1983; Kollander 1993; Callahan et al, 1995). The anecdotal, non-probability sample, study design is often used for description or exploration of a given situation. The sample is usually formed from volunteers, making it difficult to generalise the results to the general population. There is a risk that people taking part in such a study are different in some way than those who choose not to participate. One strategy could be to choose individuals from particular subgroups of the general population that are at risk, because they are highly exposed or more susceptible. The selection of a reference or control group should be considered. A reference group should be chosen from a comparable population of unexposed persons who do not differ from the exposed group in any substantial way in relation to age, gender, smoking, etc.

Sample size and power considerations

Sample size and power calculations should be carried out in the design phase of a study in order to increase the abilities to test the desired hypotheses of the study. The sample size refers to the minimum number of persons needed to be able to show that there is a statistical difference between exposed and unexposed or less exposed people. The smallest difference in exposure that is scientifically worth detecting based on measurement limit or scientific principles, must be determined and used to decide the sample size required. The smaller the difference in exposure between groups, the larger the number of people required in the study to be able to distinguish this difference. In some studies, the investigators

may be satisfied with rough estimates of the number of individuals having elevated exposures to certain pollutants. It may not matter whether the estimates are wrong by 5 or even 10 %. In other studies the researchers may need much more precise and accurate information. Generally, the way to get more precise and accurate exposure estimates is to increase the sample size.

In practice, there is a further trade-off between the ideal sample size and the expected cost of the study. There is thus no simple rule for selecting a sample size that can be used for all exposure assessment studies. A rule of thumb sometimes used is that for a human exposure study, the total sample should contain at least 50 individuals from the target population. Suppose, however, that the investigators want to focus only on people who have high exposures to a specific pollutant, perhaps because of their occupations or use of cooking fuels. If 10 % of the overall population were highly exposed to this pollutant, a sample of 50 individuals would only include about 5 persons with high exposures. This would not be a large enough group to draw valid conclusions about their characteristics. Rather, in this particular example, a sample of 500 persons would be needed to produce 50 highly exposed individuals. Another approach would be to specifically choose the potentially highly exposed people and study their exposure characteristics.

The power of a study refers to the ability to detect a difference in exposure between groups with a defined level of confidence (usually 95 %). It depends on the alpha (α) level (the acceptable probability of incorrectly concluding that there is a difference), the size of the difference to be detected, the underlying population variability and the sample size. A power of at least 0.80, which means that there is an 80 % chance of detecting a specified difference in exposure with 1- α confidence, i.e. a 95 % level of confidence when α is 0.05. Generally, the larger the sample size, the greater the power of the study.

Sample size and power calculations can be performed using statistical computer software, such as EPIINFO, developed for and distributed by WHO. It is often wise to consult a statistical expert to accurately determine these parameters for a particular study. Readers wishing to study the subject further should consult a statistics/epidemiology textbook containing information on study size and power calculation. A practical manual on how to determine sample size in health studies has been published by WHO (Lwanga and Lemeshow, 1991).

Study plan

What should be measured?

Identification and assessment of which specific hazards the population may be exposed to should be carried out. Existing data should be explored and considered in the study plan. Hazard assessments of several agents are for example given in the International Programme on Chemical Safety (IPCS) Environmental Health Criteria Series, published by IPCS/WHO (chapter 10, p. 171).

What is the source(s) of the hazard? Is the agent to be measured chemical, biological, or physical? Is there a single agent to be measured, or multiple agents, or a mixture? The investigator needs to decide what data should be collected, for example environmental or personal samples, and which exposure routes should be considered, for example inhalation, ingestion or dermal uptake. Perhaps all routes of exposure should be measured in order to decide which exposure route is the most important. For some agents, a multimedia, multiple pathway exposure assessment approach may be needed. Surrogate (or proxy) exposure variables can sometimes be used when true exposure cannot be measured. A surrogate exposure variable could be the distance from a source of exposure, for example a road or an industry. It could also be the presence of a specific source at home, such as a gas cooker emitting nitrogen dioxide, or the presence of smokers in the household, or indoor lead-based paint. This type of information is often collected via questionnaires.

Where should the study take place?

Is the study to be performed local, regional, national, international or global? Is the exposure that is to be assessed source-specific or site-specific? Where do people live or work in relation to the source? Parameters such as geographical position, altitude and meteorology might have to be considered. For example, people living in warm regions of the world need to drink more water or other beverages than the average person in the more temperate parts of the world, and therefore may be more exposed to drinking-water contaminants.

When should the study be carried out?

There may be for example daily, weekly or seasonal variations in exposure patterns that need to be considered. Furthermore, the time-span of the exposure assessment must be long enough to cover the time period of interest for the

potentially associated health effects. Is the issue acute effects from current exposure or long-term effects from cumulative exposure? Is long-term exposure, averaged over months or years, or short-term peaks more relevant for the health outcome?

How should samples be collected?

A strategy for sample collection should be developed. A decision should be made on how to collect the specific media, the process of sampling, and timing of sample collection. Should samples be collected repeatedly over time? Should a composite sample be created, for example soil samples from a contaminated area? There are certain limitations in analytical equipment that should be recognised. Are techniques available to detect the agent of interest? Are the sensitivity, accuracy and precision of the available analytical technique high enough? Is the analytical method sensitive enough to measure the concentration levels present in the study area? It is important that the investigators understand the basic concepts behind collecting various media and the limitations of different sampling methods and strategies. It is equally important to understand the parameters that influence the actual exposure from specific media (Chapter 2, p. 25). The investigator must also consider the representativity of the collected samples, i.e. whether the collected samples represent the actual exposure.

Data preparation

An often-neglected part of the data collection procedure is the preparation of data files for further analysis. It is often useful to include data preparation procedures at an early stage in the study design. Nowadays, personal computers are commonly used for the data entry and analyses. The process of feeding the data into the computer should therefore be considered in the study plan. Usually data are keyed into the computer by the field staff. To avoid errors in the data entry, the forms used should be easy to understand and the data logging personnel should not be required to perform interpretations. Interpretations made at the data entry stage are bound to introduce errors, unless the investigator prepares the data.

In large studies it may be of great advantage to automate data entry. Large surveys using questionnaires may benefit greatly from the use of the OCR (Optical Character Recognition) technique, in which the questionnaire forms are auto-

matically scanned into the computer and the text translated into a form suited for further analyses. The design of the questionnaire forms must be adapted for the OCR procedure. Measurements of environmental pollutants or laboratory analyses of biological specimens may be directly logged by the measurement instruments, thus avoiding the manual element in the data entry procedure.

It is often recommended that every data record is associated with a personal identification number (PIN) so that appropriate records (from for example questionnaires, laboratory analyses, etc.) can easily be linked together. Some countries (such as the Scandinavian countries) have the benefit of a unique PIN assigned to all citizens. In other countries, similarly, social security numbers or insurance identification numbers may be used. If these possibilities do not exist, specific PINs may be constructed for the particular study.

Pilot study

It is often wise to conduct a pilot study prior to a full-scale study. A pilot study may include a relatively limited group of people selected from the most exposed population and perhaps a small reference group of unexposed persons. The pilot study is useful for evaluation of the procedures in the field and to establish if there are any elevated exposures of concern.

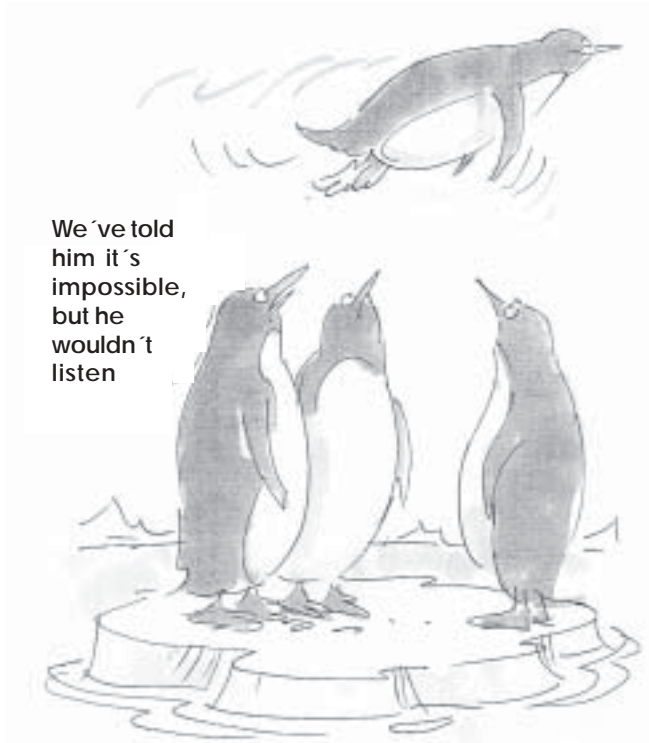
It is also important to consider if the exposure data collected from a group of individuals are generalisable to the study population (which may be an occupational cohort or the general population in a specific geographical area). If the sample is not randomly selected, it may not be representative of the study population.

If a well-designed pilot study does not reveal any probability of elevated exposures, there is no need for a full-scale study. If high exposures are certain, immediate action to reduce exposures should be initiated. An evaluation of the impact of the intervention in reducing exposure should be made.

Limitations and sources of errors in human exposure assessment

The total uncertainty or variance in the derived estimates of exposure consists of several components:

- *Population sampling error.* The mean of the population sample is not identical to the mean of the total population from which the sample was drawn.
- *Monitoring error.* Refers to the error in the concentration measurements of an agent to which a subject has been exposed. The issue of analytical errors is discussed more in depth in Chapter 6.
- *Non-participation error.* The exposure of non-participants can be significantly different from that of the participants. This error cannot usually be estimated, and can only be minimised by increasing the participant rate. However, a study of non-responders can often give a good picture of the magnitude of error introduced by a low participation rate.
- *Information error.* The study subjects may provide incorrect information on questionnaires and time-activity diaries. This leads to an error in predicting their exposure. For example, a diary may incorrectly state that between 5 and 6 p.m. the study subject was in a home where a gas cooker was being used. If, in fact, a microwave oven was used, the exposure to combustion pollutants such as NO₂ would be overestimated.
- *Mis-classification error.* Failure to correctly classify exposures in epidemiological studies will almost always reduce the observed relative risk if the mis-classification is random (not dependent on the health outcome under study). If mis-classification is systematic, the error in relative risk may be either positive or negative.
- *Selection bias error.* If subjects enrolled in a study are not representative of the target population, bias may result. A rigorous sampling procedure and strict supervision can eliminate this. For example the survey design may call for three repeat visits on different days at different times to a home before



If subjects enrolled in a study are not representative of the target population, bias may result.

another subject is chosen to replace the unreachable occupant. If an interviewer is lazy, the home is hard to reach or the neighbourhood is unsafe, they may skip the second and third visits, saying that they were made and that none was at home. This could reduce the inclusion of people who live in a certain area, or who work at night and were not at home on the evening when the interviewer made the first visit. The more demanding the participation in an exposure study, the less representative the population will be and results have to be adjusted for such biases.

- *Participant performance (Hawthorne effect error)*. When a subject carries a personal monitor or collects a duplicate diet he may alter his activity pattern either deliberately; “I wonder what would happen if I stand behind an

idling car?" or subconsciously: in a restaurant, a choice of food for lunch and duplicate diet collection that does not need refrigeration of the duplicate sample. The subjects' activities and diets may be different than their normal patterns, but may be incorrectly interpreted as normal. If one person in a hundred intentionally stands behind an idling car to obtain a high exposure, it may be estimated that 1 % of the study population has such a high exposure. This error can be minimised by giving strict instructions to the study participants that they should make no changes in their normal behaviour, and by explaining to them how failure to do so can bias the study outcome.

It is important to note that the impact of errors depends on the question to be addressed and the study design chosen to answer the question. For example: to establish the association of personal $PM_{2.5}$ exposure on the frequency of respiratory symptoms, the use of a non-representative selected population may be a valid approach. The assessment of population exposure distributions for $PM_{2.5}$, however, may suffer considerably from selection bias, requiring respective adjustments.

Important requirements for improvement of human exposure information have been outlined by Graham et al (1992; Table 6).

Table 6. Important requirements for improvement of human exposure information (Graham et al, 1992).

There is a need to:	In order to:
Collect data over time	Establish a baseline to which future data can be compared
Establish standard methods and protocols for data collection and for quality assurance/quality control	Make possible comparisons between datasets
Develop statistically representative sampling data	Allow extrapolation beyond the individual study
Collect more measurements of exposure	Develop, validate and refine human exposure models
Collect data over appropriate time frames	Support epidemiological studies. Exposure data must be collected over time frames that are consistent with the health effects of concern.
Characterise total human exposures	Allow evaluation of total exposures to individual and multiple pollutants, and to allow identification (and relative contribution) of key sources of exposure
Characterise exposures to pollutant mixtures	Understand exposures to pollutant mixtures
Identify high-risk groups	Identify biologically susceptible subpopulations, and those with the highest exposures
Address environmental inequities	Identify regional, ethnic, or socio-economic differences in exposure and health effects for identification of subpopulations likely to receive high exposures
Develop distributions of exposure	Allow characterisation of variability and uncertainty in exposure parameters, estimates, and measurements, instead of being forced to rely on conservative assumptions

Intentionally blank

After reading this chapter you will:

- Be able to describe different approaches to assessing exposure and dose
- Be familiar with the advantages and disadvantages of different methods for assessing exposure and dose
- Understand the special features of using different human indicator media

Questionnaires

Questionnaires have been used extensively for exposure assessment in the past and will continue to be used. Questionnaires can be used to obtain information of individual characteristics as well as relevant exposure factors and time-activity patterns. Questionnaires can provide information on the existence of exposure sources and other characteristics in a community or an industry, and can also be used to categorise exposure - for example asking subjects if they ever were exposed to environmental tobacco smoke (ETS). An example of a questionnaire is given in Chapter 9, p. 136. To design a questionnaire is not an easy task. Standardised questionnaires, including questions that have been tested and validated, are often available and should be used whenever applicable. This saves a lot of work and money, and is important for comparability of study results. If previously validated questions cannot be used, questionnaire validity should be assessed. If there is no gold standard available to test the validity, a test-retest study may at least provide information about the reliability of a questionnaire. Investigators involved in questionnaire design issues should study the subject more in depth, see for example Armstrong et al (1992). This section is to some extent based on that book and gives only the basic ideas of the considerations to be made when designing a questionnaire. One of the most common methods for exposure assessment in epidemiological studies is the self-administered questionnaire. Studies using questionnaires can be performed at a relatively low cost and do not require a large staff.

On the other hand, the questionnaires must usually be short (to increase participation rate) which decreases the amount of information that is possible to collect. The participation rate is crucial to the usefulness of the questionnaire. If a questionnaire yields a low participation rate, there is always a risk of selection bias, in that the individuals who have participated may have done so for specific reasons. If for example, the participants have filled in the questionnaire because they know that they are exposed to a certain environmental hazard, the answers may not be representative of the study population.

In another situation, some individuals may have chosen not to participate, because of certain life-style factors (heavy smokers or drinkers), which similarly will compromise the representativity of the study and may grossly distort the exposure assessment. The participation rate to mailed questionnaires varies greatly between countries. In the USA the participation rate for mail surveys is commonly near 75 % and in Sweden often over 80 %. In developing countries, on the other hand, the participation rates are usually lower.

The existence of an efficient postal system is of course necessary if mailed questionnaires are to be used. In the absence of a good postal system, personal interviews may be a feasible alternative. The participation rate increases considerably if the survey is carried out by personal interview, but as a consequence the costs naturally increase. Self-administered questionnaires work best in educated populations but are less useful in uneducated groups and in elderly people. In some populations such as children, direct observation of exposures and activity patterns can be useful for validation of the collected data.

Questionnaire design

The questionnaire should be designed to obtain relevant and accurate exposure estimates. The questionnaire form should be easy to understand to ensure a high degree of participation in the study. Only questions that are necessary for the study should be included in the questionnaire form. Questions that could be answered by means other than the questionnaire (for example through available records) should be excluded. When many researchers with different interests are involved in the design, the initial questionnaire may be very long, since it is tempting to include questions covering all the various research interests of the participating scientists. The project manager must ensure that only questions relevant for the present study are included in the questionnaire.



How long should an ideal questionnaire be? It has been suggested that self-administered questionnaires should not exceed 12 pages. The length of the questionnaire is, however, highly dependable on the specific study, but the objective should be to keep the form as short as possible. If the data are collected by an interviewer, the length of an interview should also be kept as short as possible and generally not exceed one hour over the telephone or two hours in a personal interview situation.

Questions should be detailed enough to allow translation into exposure data. Each relevant exposure should be possible to distinguish from other exposures that may be correlated to, for example, a disease under study. The nature and complexity of the questions may also create difficulties in getting the information from the participants. If the participants are asked about events in their lives that happened a long time ago, the risk of recall problems is great. Complex questions are naturally more difficult to answer than simple ones and add to the uncertainty of the answers. Some types of questions may make the participant unwilling to give correct answers, for example questions about sex life and drug use. Both the length of the questionnaire and the nature of its questions may give rise to lower participation rates and/or less good data quality if, for example, the respondent chooses to disregard part of the questionnaire.

Types and contents of questions

The questions asked in a questionnaire may be open-ended or closed-ended. Open-ended questions provide no given answers in the form, whereas closed-ended questions are questions for which a range of possible replies is given. Open-ended questions should be used for recording simple facts when there are a large number of possible answers (e.g. age, number of cigarettes smoked per day). Many researchers prefer, however, to use categorised closed-ended questions as an alternative (for example <10,10-19, 20+ cigarettes per day). The main advantage of using open-ended questions is that information loss is avoided. The loss of information is, however, usually negligible. An advantage of using closed-ended questions is that recording of the data may be made easier, for example, through computerised scanning of forms. If closed-ended questions are used, the answer alternatives should be clear and mutually exclusive if only one answer is to be selected. Open-ended questions may be used in a pilot phase to create reasonable closed-ended questions.

It is important that the investigator knows what he or she is asking questions about. This may seem obvious, but the researcher may not know all aspects of the possible exposures. In such cases the researcher should discuss the matter with experts in the particular field to ensure that the questions asked in the questionnaire are relevant.

Question language and format

The language used in a questionnaire should be clear, easy to understand and familiar to the respondent. This is particularly important in occupational epidemiology, where the correct names of industrial processes and manufacturing procedures are necessary to get the correct exposure information. Leading questions should be avoided so as not to give the impression that a particular answer to a certain question is the “correct” one. Double negative questions should also be avoided. The answers should be easily transferable into a computer with a minimum risk of errors in the data entry. The standards for checking boxes in a questionnaire vary between countries. In the English-speaking countries, boxes are usually checked using tick-marks, whereas in Scandinavia, crosses are used for the same purpose. If possible, the answers should be directly readable by an optic scanner, which greatly increases the speed and security of data entry. Scan-

ners can usually read checked boxes and numbers without difficulty, while open-ended questions resulting in free text are more difficult to read, categorise, analyse and interpret.

Questionnaire structure

An introductory letter explaining the study should accompany the questionnaire. The letter should assure the participant of confidentiality and point out that participation in the study is voluntary, which is usually a demand from the ethics committee approving the study. The respondent is assumed to have given his or her informed consent if he or she answers the questionnaire. Questions should be grouped in logical sets. Most questionnaires start with a number of socio-demographic questions. Then the questionnaire should focus on each agent under study, in an effort to assess the exposures for each relevant time interval. It is then often necessary with a detailed section on smoking history. Finally, a group of health related questions should almost always be included.

It is often wise to test the questionnaire on friends or relatives and then try it in a more elaborate field test, using a subset of the study population before launching the questionnaire in the main study. As a result the questionnaire may be revised if some questions seem to be difficult to answer and/or give misleading replies.

Time-activity data

In order to assess human exposure to environmental or occupational contaminants accurately, it is necessary to get an estimate of where, and how, the study subjects spend their time, so-called time-activity patterns. Time-activity data are collected via questionnaires, diaries, or interviews, or by direct observations or video recording, or by the use of electronic loggers. Time-activity patterns naturally vary between countries with different climates and levels of economic development. Until now, however, most studies using time-activity data have been performed in industrialised countries.

Time-activity data have most commonly been used in studies of health effects of air pollution, and of physical factors such as solar UV radiation and electrical and magnetic fields. However, time-activity data are also applicable when as-

sessing food, soil and dust, and water ingestion. For example, a farmer is obviously more or less exposed to agricultural pesticides depending on his use of pesticides, but also for example depending on the type of activity performed, the type of machines and technical equipment used, the use of protective gear or clothes, the season and the climate.

Using questionnaires

Commonly, exposure varies over time and thus the questionnaire should take into account different time periods and assess the correct exposure for each appropriate time interval. The most common variable recorded in this way is smoking. Usually, the investigator asks for the start of the daily smoking period and the number of cigarettes smoked per day for various time periods (often ten-year intervals). If average long-term time-activity patterns are of importance, subjects may be asked retrospectively for longer periods.

Using diaries

Diaries may be used where the subjects state how they spend, for example, each 15-minute period during the work-shift or during their leisure time. Time-activity data can be combined with microenvironmental measurements to estimate personal exposure integrated over a certain period of time (Box 13, p. 97).

Environmental monitoring

Environmental monitoring refers to repeat observations, measurements and evaluation of pollutant concentrations in environmental media such as air, water, foods, soil and dust. Environmental monitoring can be regular, such as national monitoring networks, or occasional, for specific studies. It may cover one site or a geographic area. National monitoring networks often include air, water and food. Environmental monitoring may be undertaken for several reasons:

- To assess compliance with exposure standards
- To observe changes over time in pollutant concentrations
- To monitor the effectiveness of environmental or industrial control measures, such as changes in process or ventilation, in reducing exposures
- To assess the degree of current approximate human exposure to certain pollutants

Probably the most common reason for obtaining environmental samples is to determine whether concentrations of the measured substances are within current standards. Estimates of human exposure to environmental pollutants are based on concentrations of the pollutant found in the environmental media and assumptions made about how much of the media or the pollutants gets into peoples' bodies.

Usually in exposure assessment, data collected for some purpose other than a specific study have to be used, but sometimes environmental monitoring is carried out for a particular study. If this is the case, the strategy of data acquisition can be planned accordingly. In addition to air, water, food, soil and dust, other sources may have to be considered in a sampling protocol. Exposure to certain pollutants may arise from the use of household products such as lead-glazed ceramics used for foods, and chemicals such as pesticides, medicines, and cosmetics, which may have to be included in the study plan.

It is advantageous to use standardised guidelines for environmental sampling procedures for various environmental media, if available, in order to achieve comparability between studies. Number and distribution of sampling points, as well as sampling duration and frequency, must be determined in order to adequately cover a study area and to receive representative samples. The number of sampling points depends on the size of the area to be covered and the expected variability of the pollutant concentrations. Some pollutants are more uniformly distributed through the environment than others and could be measured with relatively few sampling points. For example, respirable suspended particulate matter is more homogeneously distributed in a city than total suspended particulate matter.

Air

Monitoring in air requires sampling of the particulate and/or gaseous phase of the agent under study. Usually, fixed-location monitors are used. The location should be chosen carefully, with particular consideration being given to distance from emission sources, direction, and speed of airflow. Fixed-location monitors are often placed high above the ground (3-10 m) to avoid contamination for example during street cleaning.

In many countries, environmental concentrations of various air pollutants are regularly monitored. Monthly and yearly averages are usually reported. Such data are very useful for examining status and trends, and for national and international comparisons. As an example, Figure 16 displays the decreasing trend for some air pollutants in Stockholm, 1980 - 1995.

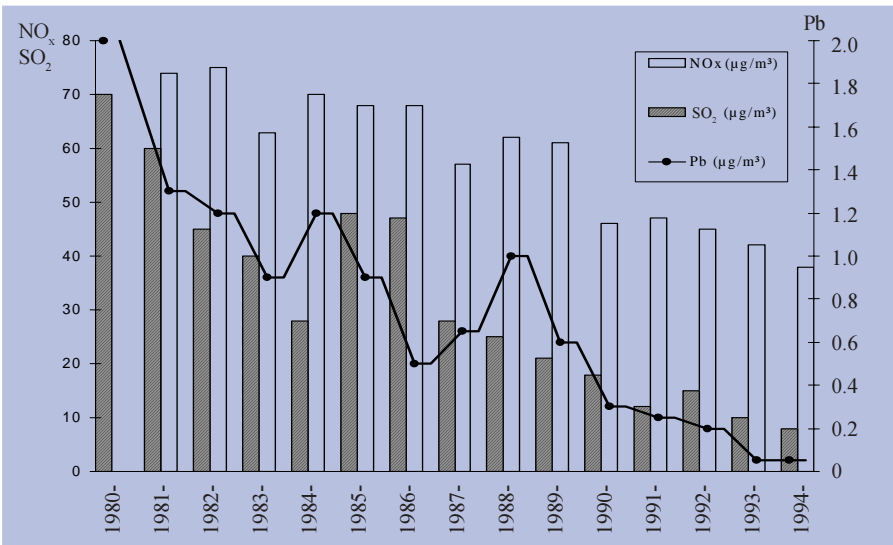


Figure 16. Trend of decreasing concentrations of some air pollutants in Stockholm 1980-1995.

However, the average outdoor concentration of an air pollutant may not reflect true exposure. People usually spend most of their time indoors, and sometimes have additional exposure at their work place or at home. Nevertheless, relatively

crude data on ambient air quality have been used in several epidemiological studies to link exposure and effects.

In urban air there is a great number of potentially harmful agents, such as sulphur dioxide, nitrogen oxides, carbon monoxide, volatile organic compounds and ozone. Some of the potentially harmful substances in ambient air may not be measured or may not even be known. Under such circumstances it may be useful to measure a surrogate, which acts as an indicator reflecting the level of the air pollutant concentration, for example particulate matter. Indeed, an association between the average concentration of airborne particulate matter and mortality has been observed, even at relatively low levels of air pollution. Cohorts of adults living in six US cities, The “Six Cities Study”, were followed for approximately 16 years (Dockery et al, 1993). The cities were characterised by different levels of long-term exposure to airborne particulate matter. Even though the levels of particles having an aerodynamic diameter of less than 10 μm (PM_{10}) met the US Air Quality Standards in each of these cities, mortality in the most polluted cities was found to be higher than in the least polluted. As data on potential confounders such as smoking and occupational exposures were available for each individual in the study, the analysis took into account confounding from these factors. Figure 17 shows the relationship between mortality and long-term exposure to $\text{PM}_{2.5}$ in the six cities examined.

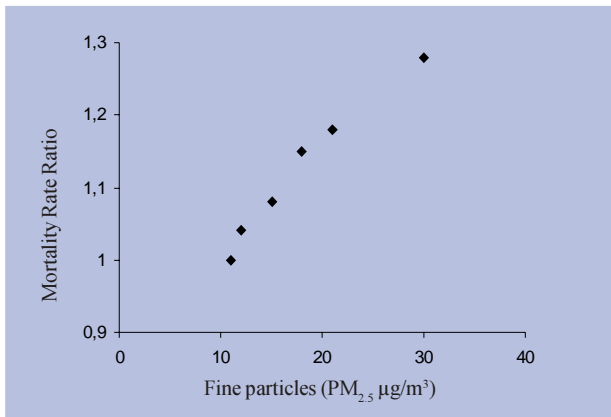


Figure 17. Estimated adjusted mortality rate ratios in six US communities in relation to concentrations of fine particles in air (data from Dockery et al, 1993).

Microenvironmental air monitoring

Microenvironmental monitoring involves measurements of air pollutant concentrations in the locations where exposure takes place (NRC, 1991b). These locations may be:

- Outdoors - urban, suburban or rural
- Indoors - work places, industrial or non-industrial
- Indoors - residential (homes), commercial (shops), public (sport arenas) or institutional (schools)
- Indoors – transportation, private (cars) or public (buses, trains, aircraft)

Often, the physical and chemical factors (for example, meteorological conditions and ventilation rates) that control air pollutant concentrations in microenvironments are measured, although this is not necessary to determine exposure. Monitoring studies can use long-term sampling at one location, or spot samples in several locations. A wide range of active and passive samplers is available.

Food

The main reasons for monitoring foods are regulatory and for dietary intake assessment. Surveillance of food contaminants is a priority of national authorities and international organisations. Identification and monitoring of critical points in the food chain is high on the list of recommendations (FAO/WHO, 1984a). Food monitoring data can be used to (Gheorghiev, 1991):

- Prevent contaminated food from reaching the consumer
- Indicate the need for measures to reduce food contamination or keep it below specified statutory limits
- Localise sources of food contamination
- Establish or check maximum residue limits for chemicals in food
- Estimate the intake of contaminants via food
- Correlate levels in the environment or body fluids with the amount in food

Food monitoring for dietary intake assessment is described at p. 81.

Drinking-water

Contamination of drinking-water may occur by percolation of toxicants through the soil to ground or surface water used as drinking-water supplies. Addition of substances to treat water (for example chlorination) and leaching of materials from plumbing systems may also contaminate drinking-water.

In assessing the exposure to substances in drinking-water, a distinction can be made between substances unlikely to change within a distribution system and those likely to change. For substances unlikely to change (e.g. pesticides contaminating the water supply), it is sufficient to sample water entering the distribution system, while for substances likely to change (e.g. metals from the plumbing system), sampling at the consumer's tap is necessary. The selection of taps for sampling is not straightforward. If systematic variations are not suspected, random sampling should be employed. If systematic effects are expected they should be taken into account in designing the sampling programme.

When drinking-water is sampled from the consumer's tap, the concentration of chemicals may depend on the residence time of water in the pipe, on the type of pipe material and on the water flow rate during sampling (Dobbs and Hunt, 1991). Thus, the timing and manner of sampling is critical. For example, lead samples in domestic plumbing taken after overnight stagnation will give higher lead concentrations than samples taken after prolonged flushing. Thus, neither of these samples reflects true potential exposure, and random daytime sampling will most likely give the most valid exposure estimate.

In cases where random fluctuations in concentrations occur, the variations often follow normal or log-normal distributions (Chapter 7, p. 116). For normally distributed fluctuations, the time of sampling is relatively unimportant, and the number of samples is determined by the required confidence limit of the mean and by the magnitude of the random variations. When systematic variations occur, the sampling frequency should not be a multiple of the frequency of any cyclic systematic variation, in order not to bias the mean. If a measure other than the mean is required, for example the 95th percentile, the number of samples required will be much higher to provide an equivalent measure of confidence.

Soil

Soil may be a source of exposure to many toxic substances, particularly in children due to their normal oral behaviour. Soil can contain many different types of pollutants, for example persistent agents such as metals or PCB, which can contribute to exposure via ingestion or dermal uptake, or volatile organic substances which can contribute to exposure via inhalation. Some contaminants are firmly bound in the topsoil level (e.g. lead), and are thereby available to humans via ingestion or dermal contact. Others are transported downwards through the different soil layers and may thereby contaminate groundwater, or they may be taken up by plants (e.g. cadmium and caesium). Surface soil samples are collected at contaminated sites to estimate the degree of contamination of soil available for contact or uptake by plants. Soil core samples are collected to provide information on the degree of soil contamination, and how pollutants are transported in soil.

A contaminant in soil is generally not homogeneously distributed, which makes it difficult to collect representative samples. There are not yet any general guidelines for soil sampling collection. Basically, there are two possibilities:

- Grab sampling
- Composite sampling

Grab samples are taken at a particular time and place, and analysed individually to cover variations in soil contaminant concentrations. Composite samples are pooled samples taken from a predefined area. Usually five samples are taken in a standardised manner from an area of one square metre and the composite is analysed.

Measurements of contaminant concentrations in soil combined with information on contact rates (e.g. soil ingestion rates in children) provide estimates of exposure (p. 83). It is important to investigate the chemical and physical properties of various soil pollutants and also their bioavailability, i.e. how efficiently they are absorbed in the gut after ingestion, in the lung after inhalation, or through skin if applied.

Dust

House dust may be a significant source of exposure to many toxic substances, particularly in children due to their oral behaviour. Unintentional ingestion of house dust has been shown to contribute substantially to children's lead exposure in contaminated areas (WHO, 1995). Toxic substances in house dust can originate from activities in the home or can be tracked into the home from road dust, soil, or work sites. House dust may contain many toxic substances such as metals (e.g. lead), pesticides (from outdoor sources or household products such as insecticides), fibres (e.g. asbestos), biological matter (e.g. bacteria or allergens), or other material.

Many dust sampling methods have been described in the literature, but there has been little standardisation of methods. Thus, there is as yet no standard for sampling dust. This means that results from one study using one method of dust sampling are not comparable with the results of another study using another method. Therefore, it is important that sampling methods are well described when results from dust sampling are reported.

There are three main categories of dust sampling:

- Wipe sampling
- Vacuum sampling
- Sedimentation methods

The most commonly used wipe sampling method uses pre-moistened paper tissues (Kleenex or similar), to wipe a defined area of typically 0.1 m². The person collecting the sample should wear a clean disposable glove on the hand holding the paper. The paper tissue is then sent to the laboratory and analysed for the substances in question. In some studies, pre-weighed wipe material has been used. The material is re-weighed after the wiping procedure, and the weight of total dust can be calculated.

Dust can be collected using commercial household vacuum cleaners or specially designed vacuum sampling devices. A specified area is vacuum cleaned and the dust collected in the bag or on a filter inside the vacuum cleaner is analysed, before or after fractionation of the dust. The rationale for fractionating dust is

that the small particles are more likely to stick to children's hands and thereby reflect the agents to which children are potentially exposed.

Sedimentation methods involve measuring the amount of dust that settles on a clean, pre-weighed surface over a given period of time. A clean, flat plate or a pre-weighed section of carpet is placed on a shelf, a window sill, or on the floor. After a specified period of time, the settled dust is analysed in a laboratory.

The exposure to a substance in dust depends on the total amount of dust available for exposure and the concentration of the substance in the dust, as well as the actual amount of dust ingested or inhaled.

Microorganisms and biological particles

Human exposures to microorganisms (e.g. fungi, bacteria, and mites) may result in allergic, toxic or infectious diseases. Humans are continuously exposed to microorganisms through airborne dispersion, ingestion or direct contact.

There are three basic approaches for the exposure assessment of microorganisms and biological particles:

- Observational sampling,
- Reservoir sampling
- Air sampling

Observational sampling uses sensory perception to collect data about potential sources of exposure to biological particles (e.g. visible fungal growth). Reservoir sampling refers to the collection of bulk material (e.g. dust, soil, and water) to estimate the potential exposure.

Air sampling or reservoir (dust) sampling have been used to measure levels of house dust mites and their allergens, allergens from cockroaches and pets, fungi, bacteria and pollen. At present no reliable information is available that will support adoption of a standardised method for air sampling of these microorganisms and biological particles. Dust sampling for measurement of the level of mite infestation is accepted and recommended. Standardised sampling procedures to measure house dust mites and their allergens in house dust have been proposed (for example, Commission of the European Communities, 1993; Dreborg et al,

1995). The same methods can be used for allergens derived from cockroaches and pets, fungi and spores, bacteria and pollen grains.

Personal monitoring

Personal monitoring refers to repeated observations, measurements and evaluation of pollutant concentrations in samples collected from an individual's immediate environment. Personal measurements of an individual's exposure to a contaminant or a class of contaminants have been used extensively by industrial hygienists in occupational settings for air contaminants. Personal monitoring provides measures of exposures across the various microenvironments where individuals spend their time, as well as data on variations in exposure concentrations between and within individuals. When combined with biological monitoring, personal exposure data can link exposure concentrations with internal dose. For example, air CO concentrations can be linked with blood carboxyhaemoglobin levels, and air nicotine concentrations with blood, urinary, or salivary levels of cotinine, which is a metabolite of nicotine. If the toxicokinetics of the pollutant measured are known, the absorbed dose and the target organ dose may be estimated. Personal monitoring is usually time-consuming and expensive to carry out.

Air

A personal air monitor carried by an individual provides much more detailed information about the exposure than fixed site monitoring. The personal sampler is usually placed close to the mouth in the breathing zone and provides measurements of the concentrations of the air contaminant inhaled. Samplers can be active or passive and can directly record the concentrations in breathing zone air or collect time-integrated samples of specific contaminants for specific time intervals (from hours to days). Active samplers use small pumps either to draw air (usually at a rate of two litre/min) through a collection medium (for example filter or vapour trap) or to draw air through a direct-reading detector. Active samplers are useful when measuring respirable particles. Recent advances in active personal monitors include miniature denuder monitors for assessing personal exposures to acid particles and gases. Electrochemical sensors for active personal monitoring have recently been reported in use for nitrogen dioxide, CO

and ozone. Passive gas samplers use diffusion or permeation to concentrate gases on a collection medium. Passive samplers (badges or tubes) for air contaminants such as volatile organics, formaldehyde, nicotine, nitrogen dioxide and other gases have been developed. Many of these monitors provide the sensitivity and specificity necessary to conduct personal air-monitoring exposure assessment at a reasonable cost.

The drawback with personal samplers is obviously that they may be somewhat uncomfortable, and therefore cannot be used for long periods. This is particularly true for active samplers, which are rather noisy. It is also possible that a person carrying a portable device becomes more aware and as a result behaves differently than he or she does under normal circumstances (Chapter 4, p. 61).

Sometimes the monitored pollutants may be surrogate measures rather than estimates of the exposure directly associated with the health effect, which is often the case for complex mixtures. For example, traffic exhaust is a mixture of a variety of potentially hazardous agents, but ambient NO₂ measures are excellent indicators of traffic related pollution even if the measured concentrations of NO₂ are well below toxic concentrations. In an indoor environment, NO₂ is a good indicator of the level of exposure to gas cooking related agents. Thus, the NO₂ concentration collected on a passive sampler over a time period reflects total NO₂ exposure, which may partly be due to traffic, and partly due to gas cooking or other sources of NO₂ exposure. The relevant contribution of each is indistinguishable. Therefore, in such a study outdoor and indoor NO₂ assess-

Table 7. Strengths and weaknesses with stationary and personal air sampling.

Type of monitoring		Strengths	Weaknesses
Stationary/Area		Sophisticated equipment can be used. Large volumes of air can be collected, for long periods of time	Does not necessarily represent the true personal exposure
Personal		Represents personal exposure	Weight of equipment must be low. Restrictions on volume, small sample volumes. Cannot be used for long periods

ments may be more informative than personal exposure monitoring. Even more information is gained if both environmental and personal monitoring are carried out simultaneously.

Table 7 summarises some of the strengths and weaknesses of stationary and personal air monitoring.

Food and drinking-water

Monitoring of food for the estimation of actual dietary intakes of contaminants is characterised by randomised representative sampling in a country or a given area in the country, and is linked closely to food consumption data (WHO, 1985; Gheorghiev, 1991). Three basic approaches for sampling food are used:

- Sampling of individual food products
- Total diet (market basket) studies
- Duplicate portions

Individual food products are the simplest to analyse and have been used extensively to estimate intakes. The basic disadvantage with this method is that the effect of cooking on the contaminant and the consequent disposal of waste from culinary preparation and incompletely eaten portions cannot be taken into consideration.

In total diet or market basket studies, food representative of the diet of an “average” person or age/sex group is purchased, and sometimes prepared for table consumption either individually or, more often, combined in groups (composites), and analysed for specific contaminants.

The duplicate portion approach is a direct sampling technique in which an exact duplicate of the food being consumed by a person is obtained and analysed. This method is suitable for the estimation of the intakes of individuals and small groups. It provides the most accurate estimates, because it combines results for each contaminant with the actual food consumed. However, it is limited to small population groups and it is also expensive and requires a high degree of cooperation from the study population. Storage of samples may affect unstable contaminants and create new ones.

Frequency of sampling should be timed to cover seasonal variations in the supply of certain foods or seasonal variations in contamination patterns.

It is relatively easy to measure the concentration of a pollutant in water and various foodstuffs, but it is difficult to estimate the amount of food and beverages actually being consumed. Methods to calculate the dietary intake of populations and individuals (food consumption data) include:

- *Food diary.* Recording of types and amounts of specific foods eaten, their quantity or weight, often during a 24-h period or repeated 24-h periods. Four to ten days should give a reasonable record of the actual intake
- *Dietary recall interview.* Answering questions about food and beverages consumed during a particular period
- *Food frequency.* Answering questions about the usual patterns of food intake (how much bread do you usually eat per day?)

The food diary is a prospective method, which may interfere with the study subject's everyday life, and cause a change in the food choice and food intake. The dietary recall interview is a retrospective method. In recalling past diets, ingested food items may easily be forgotten.

Food sampling and food consumption data are combined to give appropriate information on individual or population levels.

Population intake estimates can be based on data from individuals to provide an average and a range of consumption for particular food items in the population. A crude assessment of the population exposures can also be derived from food consumption of households, or areas, based on the type and quantity of food available compared with those at a later point in time. Using such methods, animal protein intake (or any other intake) in different countries and groups can be compared. The 'food balance' or 'national food disappearance methods' provide only limited information if the concentration of the contaminant of interest in basic foodstuffs is not well known. If a researcher is interested in investigating the possible association between exposure to nickel in food and the risk for oesophagus cancer, the investigator will soon learn that data on nickel in most foodstuffs are not very well known or even detectable. If detection limit values are used as tentative actual concentrations, the estimated daily intakes will be



too high. These errors, when multiplied by the average consumption of these products, may markedly affect and bias the estimated intake.

Estimation of oral exposure from drinking-water and other beverages requires assessment of the amount of water consumed and the concentration of the pollutant. Two litres of water per day

for adults and one litre per day for children (weighing less than 10 kg) are often used as default values for drinking-water intake. In hot climates, and in people with a high physical activity, the drinking-water intake may be much higher.

In addition to direct consumption, it should be recognised that tap water may be used to prepare hot beverages, during which changes in concentrations of chemicals may occur, and for cooking food, to which the chemical may be transferred from the water. The tap water supply may also be used for washing and laundering operations for example, and these may offer other exposure routes. Furthermore, assumptions must be made about the amount of tap water ingested by individuals, the amount of bottled water consumed, and changes occurring as a result of different forms of domestic water use. Questionnaire data may be unreliable for assessment of drinking habits. It has been noted in several studies that about twice as many alcoholic beverages are sold in many countries compared to what people in those countries report to consume. Obviously, people under-report their true consumption of certain foods and beverages.

Ingestion of non-food substances

Ingestion of non-food substances may significantly contribute to total exposure, which is particularly true for many metals. The frequency and quantity of exposure via the non-food route are usually very hard to determine. However, if the concentration of a metal in faeces is higher than would be expected solely as a result of the metal concentrations in food, exposure via non-food items is plausible. Examples of non-food items are medicines, toothpaste, cosmetics (e.g. lipstick), soil and dust.

Soil and dust (particles)

As mentioned earlier in this section, the ingestion of soil and dust is a potential source of human exposure to toxicants, particularly in young children. Adults may also ingest soil or dust particles that adhere to food, cigarettes, or their hands. Deliberate soil ingestion is defined as pica and is considered to be relatively uncommon. Soil and dust ingestion can be estimated by measuring the amount of dirt present on children's hands using hand-wipes, and making generalisations based on behaviour. Soil intake studies have also been conducted using a methodology that measures trace elements in faeces and soil. Certain rare earth metals present in soil, which are only present in very small amounts in food, and are poorly absorbed in the gastrointestinal tract, may be analysed in faeces to give an estimate of the amount of soil and dust ingested (Calabrese et al, 1989).

Dermal exposure

Dermal exposure may occur during a variety of activities in different environmental media and microenvironments. Exposure to water may take place during washing, showering and swimming, exposure to soil during outdoor activities and exposure to various liquids and fumes during use of commercial products. The major factors to be considered when estimating dermal exposure and uptake include the agent concentration in the media in contact with the skin, the extent of skin surface area exposed, the duration of exposure and the rate of absorption of the agent.

Dermal wipe samples or dermal pads are used for personal monitoring of exposures via the dermal route. Hand-wipe sampling and analysis procedures involve wiping of the entire hand with a paper or sponge, which may be wetted with a dissolving agent, and analysis of the agent recovered from the wiping material. Dermal pads are used to collect the agent for a specific period of time, e.g., during work shift, and the pads are then analysed. These methods have been used for pesticides and metals.

Ionising radiation

Personal radiation monitoring devices are used for continuous occupational exposure and dose monitoring. The most widely used dosimeter is the thermoluminescent detector known as the “film badge”. It measures ionizing radiation, which includes x-rays, and β - and γ -rays. The radiation dose is integrated over a period of time, usually a month.

Biological monitoring

Biological monitoring refers to measurements of concentrations of biological markers (biomarkers) in human indicator media such as blood, urine, faeces, hair or breast milk. Measurements of concentrations of potentially harmful agents in a critical organ (the organ where adverse effects are seen at the lowest concentrations) such as the brain, liver, kidneys or the skeleton, are rarely possible unless an autopsy or surgery (biopsy) is carried out. Instead, a biomarker reflecting the exposure may be measured in human indicator media. As a rule, biological monitoring of a particular agent should not be carried out without knowledge of the relationship between exposure and internal dose. Ideally, biological monitoring mirrors the concentration of the hazardous agent in the critical organ. For example, carbon monoxide bound to haemoglobin reflects recent exposure and critical concentration at the same time (Lauwerys and Hoet, 1993).

Biological monitoring provides information on the absorbed or internal dose, and the total exposure of the individual, integrated over all sources and routes of exposure. It also takes into account inter-individual and intra-individual differences in intake and uptake, as well as differences in metabolism and physical activity. Biological monitoring can therefore identify high-risk individuals or groups of individuals. The disadvantages with biological monitoring are related to the invasive sampling, the kinetics and timing of exposure, and ethical considerations. The risk for contamination during sampling and sample treatment is also quite high, due to small sample volumes and/or low concentrations of contaminants (Chapter 6, p.102).

Biological monitoring has proved to be particularly useful for assessing exposure to metals (Elinder et al, 1994) but also for more than 50 organic substances (Lauwerys and Hoet, 1993). New techniques, such as *in vivo* neutron activation

and X-ray fluorescence, have made it possible to measure metals in situ: lead in the skeleton and cadmium in the liver and kidneys. However, these techniques are still quite crude and usually offer no improvement over traditional exposure assessment methods. Further development is needed before the so-called 'in vivo' methods can be used for low level exposure assessment.

The advantages and limitations of biological monitoring in exposure assessment should be considered during the planning of a study. In situations where environmental hazards exist in complex, partly unknown, mixtures of pollutants, the focus on biological monitoring may be misleading, capturing only a specific part of a problem. In such cases, environmental monitoring may be the more appropriate approach. However, biological monitoring is important and usually more efficient at identifying the biological mechanisms and pathways of specific exposure-effect associations. Biological samples may be stored in specimen banks for future analysis.

Biomarkers

Biomarkers can be subdivided into three areas, biomarkers of exposure, of effects and of susceptibility.

- Biomarkers of exposure are indicators of exposure to a chemical and the internal dose resulting from the exposure. Biomarkers can represent past exposure, since many pollutants remain in the body for a considerable time, but they may also reflect recent or current exposure. In special cases biomarkers may even represent future endogenous exposure due to release of agents accumulated in bone or adipose tissue. The biomarker could be the contaminant of interest, its metabolites, or products of interactions between a xenobiotic and some target molecule or cell. Ideally they are specific metabolites or adducts indicating interaction with the biological system, although the parent compound will have to be measured if it remains unchanged. Adducts can be formed with protein such as haemoglobin, or if genotoxic agents are activated into reactive forms in the cells, they may bind to the DNA, forming DNA adducts. DNA adducts can be measured in blood cells, but the specificity is low. The level of DNA adducts depends on the rate of adduct formation and the rate of elimination by DNA repair processes or cell death.

- Biomarkers of effect are indicators of biochemical change of potential toxicological importance to an organism, such as beta-2-microglobulin as a marker of early renal damage. The ideal biomarker of effect should detect early changes after exposure before irreversible health effects occur.
- Biomarkers of susceptibility may be used to detect individuals with certain susceptibility to exposure. Genetically determined enzyme polymorphisms, such as the slow and fast acetylator phenotypes in humans, may be used as biomarkers of susceptibility.

Common media used in biological monitoring

Urine and blood are the media most commonly used in biological monitoring, but other media that are relatively easy to obtain, such as hair, faeces, or breast milk have also been used (p. 92). It is important to consider the timing of sampling when interpreting data: a blood sample may represent 10 seconds of blood flow; a urine sample may represent 10 hours of collection in the bladder; and a hair sample, 10 cm in length, represents 10 months of hair growth.

Urine

Urine samples are often used in biological monitoring. They are easy to collect in large volumes, and the procedure of sampling is non-invasive. For many xenobiotics, urine is an important route of excretion, and frequently the predominant one.

The concentration of a substance in urine is influenced by a number of factors: the degree of dilution, the kidney function, the body burden of the substance, the metabolic and kinetic pathways, and current or past exposure. Urine is produced continuously by the kidneys as part of a complex process of water and electrolyte control. The kidney's glomeruli produce at a rate of 125 ml/min an ultra-filtrate (the primary urine) consisting of water, salts and small molecules. Large molecules such as immunoglobulins and albumin, as well as blood cells, do not pass through the glomerular filter but remain in the blood. A total blood volume of about 300 litres is filtered every day. If the glomerular filtration rate (GFR) is decreased, the capacity for eliminating toxic substances also decreases. The concentration of a substance in the urine will become lower while the body burden increases. This is the case for aluminium, a pollutant that is normally excreted in the urine,

but which accumulates in the body of those suffering from severe renal impairment.

Essential fluids and substances, for example some salts, amino acids, sugar and small proteins, are reabsorbed from the primary urine (more than 99 %) in the kidney tubules. Substances that are not reabsorbed remain in the concentrated urine and are eliminated from the body. Some substances are actively excreted from the blood into the urine, making the total elimination of waste products still more effective.

Many toxic substances and drugs are bound to small proteins, and are reabsorbed in the tubules. However, if reabsorption fails due to kidney tubular damage, the urinary excretion of the substances increases. This has been shown to occur for cadmium and copper, for example.

If possible, all urine produced during a defined time period, for example 24 hours, should be collected. The excretion ($\mu\text{g}/\text{hour}$) of a substance can then be calculated and related to the exposure or body burden. If stable results are to be obtained, the urine must be collected over a reasonably long time period. This may of course be difficult. For practical reasons, a spot urine sample is typically collected, often first morning urine, and the concentration (e.g. $\mu\text{g}/\text{l}$) is determined. The concentration of a substance, rather than the excretion rate, can be a useful measure, provided it is adjusted to a defined specific gravity, or to the concentration of creatinine in the sample to compensate for the degree of dilution (Box 12).

Blood

Blood is a transport medium. After absorption in the gastrointestinal tract or the lungs, substances are transported via the blood to different tissues and organs where they are stored, accumulated, or metabolised. Substances that have been absorbed by tissues will be released and degraded by normal tissue metabolism and once again transported in the blood, and eventually eliminated from the body. The blood concentration of a substance is influenced by the exposure and the concentrations in the tissues (the body burden). The relative importance of these two factors varies according to the substance in question and the exposure level.

A substance in the blood is bound to the red cells or to plasma proteins. For most

Adjustment of urine samples

To evaluate the concentration of a substance in urine it is often necessary to consider the degree of concentration of the urine. This is of particular importance when the urine sample is used for measuring exposure or dose, as well as the effect, for example in the form of urinary excretion of proteins. The composition of urine is usually compatible with maintenance of body water and solute content within physiological limits. A short time after consumption of a large volume of fluid, the urine will become diluted, with a low solute content. When water is evaporated, for example due to perspiration as a result of high environmental temperature or hard physical work, the urine concentration increases. The concentration of a substance in urine can be related to creatinine or specific gravity to compensate for the degree of dilution.

Creatinine (MW 113) is a metabolic product of the muscles and is excreted in the urine in fairly constant quantities. The excretion rate is higher in males, muscular individuals and those who eat a lot of meat. Young and middle-aged men excrete between 1.4 and 1.9 g creatinine/day, while the excretion in women is usually 40 % less. If the excretion is reported as microgram (or mole) per gram (or mmole) creatinine, it is possible to calculate an approximate 24-hour excretion of the substance, by multiplying it by the normal 24-hour excretion of creatinine.

The other alternative to compensate for the degree of dilution is to adjust to a defined *specific gravity*. If a urine sample has a specific gravity of 1.012, which is fairly diluted urine, and is to be adjusted to a urine with a more normal specific gravity (1.022), the following calculation should be made:

The concentration in the urine sample $\times (1.022-1.000) / (1.012-1.000)$

The factor of 1.000, which is the specific density of water, must be subtracted from both the numerator and denominator. The other decimals approximately represent the solute concentration, i.e. the degree of concentration of the urine. Independent of the method used for correction of diluted urine samples, the result is unreliable if the urine sample is very diluted (specific gravity less than 1.010 or creatinine concentration below about 0.3 g/l). A new sample should preferably be collected (Lauwerys and Hoet, 1993). The importance of adjustment for dilution is illustrated in Figure 18 (p. 90).

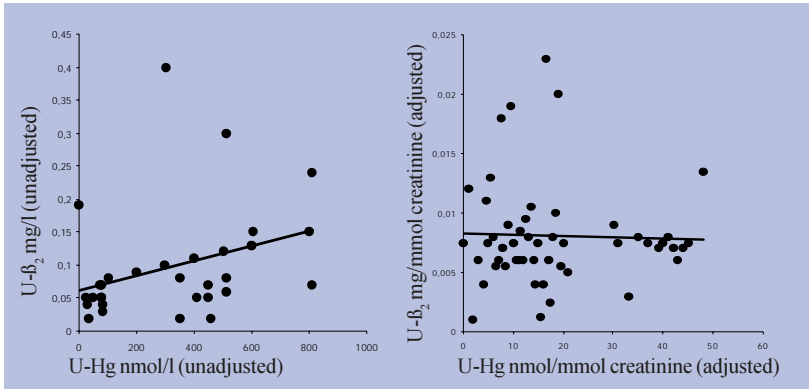


Figure 18. Urine concentrations of β -2-microglobulin versus mercury (U-Hg), unadjusted and adjusted. Without adjustment for dilution of urine (left figure) there was a significant but erroneous correlation between urinary excretion of mercury and β -2-microglobulin (data from Langworth et al, 1992).

essential metals, such as iron, copper and zinc, the body has special transport proteins, such as transferrin, ceruloplasmin and alpha-2-microglobulin. Certain non-essential and toxic substances, metals in particular, bind preferentially to the red cells. Cadmium and lead are almost completely bound to the red cells. Sometimes it may be necessary to adjust for the haemoglobin concentration, or hematocrit, when the metal concentrations between individuals or groups are compared. The concentration of contaminants in plasma is of particular interest, since it constitutes the fraction of the substance in blood that is readily available for transport in and out of the tissues. However, for many toxic substances concentrations are so low that they are very difficult to measure. Highly lipophilic compounds, for example PCB, in blood should be adjusted to cholesterol, triglyceride or low density lipid (LDL) concentration.

Sampling strategy

The concentration of a substance in biological media such as blood and urine usually varies with time. When selecting a correct marker of exposure, knowledge of the toxicokinetics of the compound or its marker is essential. Development of physiologically based multicompartiment models has improved the understanding of the dependence of external exposure and the concentration profile of the compound, or its metabolites, in the body. Elimination half-time is, in

general, the most important determinant for selecting the correct sampling strategy. For low, but constant, exposure to substances eliminated with first order kinetics, the steady state concentration in the body is reached after four to five half-times. Table 8 classifies time until steady state after continuous exposure

Table 8. Classification of compounds by elimination half-time, time to reach steady state after continuous exposure and resulting sampling requirements (from Heinzow and McLean, 1994).

Elimination ($t_{1/2}$)	Exposure until steady state	Sampling time
< 2 h	Recent	Very critical
2 - 5 h	Day	Critical
5 - 48 h	Week	End of exposure
> 48 h	Months-years	Not critical
Months-years	Lifetime	Not critical

and the importance of an appropriate sampling time.

Pharmacokinetic parameters may vary according to differences in volume of distribution. The amount of body fat affects the steady state exposure at a given rate, so that the elimination of lipid soluble compounds decreases with increasing body fat. A fat individual exposed to a certain concentration of a solvent will attain a lower blood concentration than a lean person. On the other hand, due to uptake and slow elimination from fatty tissues, the absorbed amount of solvent will be retained for a longer period of time. Exposure to halogenated dioxins can be detected several decades after the exposure due to retention in adipose tissues and an extremely slow elimination.

Figure 19 (p. 92) shows the excretion of cobalt in urine for a group of hard-metal workers. The urinary levels increase considerably during the working day. However, due to rapid excretion and a short half-time, the urinary concentration of cobalt decreases, and is considerably lower by the next morning. There is a certain accumulation of cobalt at the beginning of the week, as can be seen from the increase in morning concentrations. During the weekend, urine concentrations decrease. The exposure can be evaluated by comparing the cobalt excretion before and after work shifts. The accumulation of cobalt in the body can be evaluated by analysing cobalt in urine before and after a period without exposure, such as a weekend or vacation. These observations are similar to those concerning several other metals, such as arsenic, chromium and nickel, all of

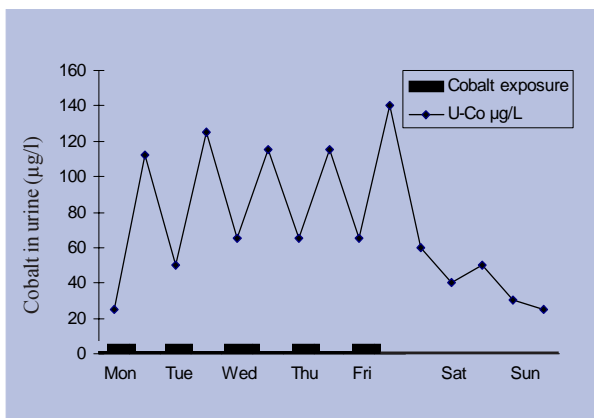


Figure 19. Excretion of cobalt in urine in a group of hard-metal workers, before and after their work-shift, during one work-week and the following weekend (Elinder et al, 1994).

which are eliminated rapidly via urine. If the substance (e.g. cadmium or lead) is firmly bound to and mainly recovered in the red blood cells, which have an average life span of 120 days, the timing is less crucial. On the other hand, timing is more crucial when monitoring a metal such as aluminium, which is transported mainly in plasma.

Other human media that can be used for biological monitoring

Hair

Hair has been used to some extent to assess exposure to metals. As the hair grows, metals from the blood and glands become incorporated in it. The major problem with biological monitoring of hair is the risk that metals from the environment have become trapped in it. For most substances, it has proven impossible to eliminate external contamination of the hair, and several studies have shown that the correlation between metal concentrations in hair and blood is poor. However, if the exposure is exclusively from food, there will be no problem of external contamination. Methylmercury, for instance, is found in high concentrations in certain foodstuffs, particularly fish. In populations consuming fish with a high methylmercury content, methylmercury is absorbed from food

into the blood and subsequently incorporated into the hair during the growth phase. A close relationship has been found between mercury in whole blood and in hair. Analysis of mercury in hair has also been of great value in studies which have correlated methylmercury exposure during pregnancy with foetal damage. By analysing methylmercury in hair, it has been possible to reconstruct the methylmercury exposure experienced by the mother during her pregnancy. Hair normally grows at a rate of 10 mm/month. Therefore analysis of different sections of a hair strand 100 mm in length will give a good indication of the blood mercury levels of the mother during the different months of her pregnancy.

Skeleton

Some metals, such as aluminium and lead, accumulate in the skeleton. By analysing bone tissue, it is therefore possible to estimate long-term exposure and total body burden. Concentrations in bone may be reported per gram wet weight, dry weight or ash weight, or sometimes in relation to the calcium content of the bone sample. It is obviously more difficult to obtain bone samples than blood and urine samples. A bone biopsy can be performed with a special instrument, under local anaesthetic. This method has been shown to be of value for estimating the body burden of lead resulting from lead exposure earlier in life. It has also been used to study aluminium accumulation in the skeleton of dialysis patients. Techniques for measuring exposure, but which do not require a bone sample, have also been developed (p.85).

Tooth enamel

Tooth enamel is of special interest as it is formed over several years during pregnancy and childhood. There is only a very small exchange of minerals after that period. By analysis of the mineral concentrations of enamel from shed deciduous teeth (milk teeth) exposure has been estimated retrospectively. Teeth are useful tissues for assessing long-term lead accumulation from prenatal exposures to the time of shedding of the tooth.

Faeces

For some substances, in particular metals, that are absorbed only to a limited extent from the gastro-intestinal tract, faeces can be used for an overall quantification of oral exposure. Skare and Enquist (1994) found that the average faecal elimination of mercury in normal humans in Sweden was 58 µg/day, ranging from 1 to 190 µg/day. These figures are much higher than the estimated daily

intake of mercury from food and water, about 2 µg. The reason for the high concentrations of mercury in faeces are losses of mercury from amalgam fillings. A linear relationship was found between the number of amalgam fillings and faecal excretion of mercury.

The faecal content of lead and cadmium can be used to estimate the total daily intake, since the gastrointestinal absorption of these metals in adults is low (about 10-15 % and 5 %, respectively; Vahter et al, 1991). The concentrations of the metals in faeces are multiplied by the amounts of faeces produced, for example per 24-hour period. A faecal marker can be used to indicate the beginning and end of faeces collection.

Breast milk

Analysis of breast milk has been very useful for following time-trend in human exposure to lipophilic chemicals, such as organochlorine contaminants as displayed in Figure 14, p. 50 (Lundén and Norén, 1998). Monitoring of breast milk has generally been carried out to estimate the exposure of the child, rather than that of the mother, but the content of lipophilic substances in the milk also represents the body burden of the contaminants in adipose tissue of the mother. Breast milk is a useful medium since most newborn children obtain all their nutrition from mother's milk. The concentration of a contaminant in breast milk is a function of parity (number of children), age, body mass, time of sampling, nutritional status, lactation period, and fat content of the milk.



Modelling exposure

Direct exposure measurements are the only way to establish unequivocally whether, and to what extent, individuals are exposed to specific agents.

However, it is usually neither affordable nor practical to measure exposures for everyone in the population of interest. Instead, a model can be used to describe quantitatively how contact occurs between individuals and hazardous agents. Basically, such a model estimates exposure by combining concentrations of the agent in a carrier medium (for example, CO in air) with individual contact time

(for example time spent in various microenvironments; Box 13, p.97). However, exposure is also dependent upon a number of influencing factors such as age, climate, type and place of home, food habits, etc. Inclusion of the most important influencing factors in the model makes it possible to evaluate relationships between pollutant exposure and explanatory variables. This can be done for example by use of statistical methods such as regression analysis.

Exposure models can sometimes provide estimates of distributions of population exposure. Monte Carlo and other statistical techniques are increasingly being used to generate and analyse exposure distributions for large groups (US EPA, 1992). Model results can be used to evaluate exposures at various points of population distributions, for example for the individuals in the high end of the exposure distribution. However, a description of statistical modelling is beyond the scope of this text.

Physiologically based pharmacokinetic (PBPK) models have been developed that quantitatively describe the process of uptake, distribution, metabolism, and excretion of substances within the body (Masters, 1991). Basically, the body is divided into various compartments, representing various types of tissues or organs. The models are used to calculate the delivered dose of a substance to a target organ by use of assumed absorption rates, metabolic level, tissue volumes, partition coefficients, elimination rates, etc.

A model needs to be validated in order to evaluate if the resulting data are accurate for the population it describes, or if the model results are to be used to predict exposure for another population or environmental setting. Basically, validation is done by comparing model predictions with field measurements independent from these used to develop the model. Validated exposure models can be used as an alternative to expensive measurement programmes by providing estimates of population exposures based on a small number of representative measurements. The challenge is to develop appropriate models that allow for extrapolation from exposure measurements for relatively few individuals to a much larger population. Validated exposure models can also predict the reduction in exposures that would occur after implementation of control strategies and regulatory approaches.

The advantage of modelling exposure is that it enables assessors to make estimates of exposure and dose with very limited data. On the other hand, the uncer-

tainty introduced by the need to make assumptions because of the limited data is a major disadvantage.

Nowadays, easily accessible and powerful statistical packages for personal computers make it feasible to examine different forms of single, combined and multiple exposure measures. This increases the possibility of disclosing true associations between exposure and effect, but also involves a risk of obtaining spurious, albeit significant, associations.

Table 9. Time spent in different microenvironments with different CO concentrations (WHO, 1982).

Time	Microenvironment	CO concentration (mg/m ³)	Duration (hours)	Cumulative exposure index (mg/m ³ * h)
00-07	Home	1	7	7
07-08	In transit	17	1	17
08-12	Office	4	4	16
12-13	Restaurant	9	1	9
13-17	Office	4	4	16
17-18	In transit	18	1	18
18-20	Shop	3	2	6
20-24	Home	1	4	4
	Total		24	93

The time-weighted integrated exposure model

The time-weighted integrated exposure model uses microenvironmental concentrations and time-activity data to calculate the exposure in each microenvironment and the total exposure from all microenvironments. The input data can be point estimates, actual data, or one can use distributional data. The equation used to calculate time-weighted integrated exposure from microenvironmental monitoring data is:

$$E_i = \sum_j^J C_j t_{ij}$$

where E_i is the time-weighted integrated exposure for person i over the specified time period; C_j is the pollutant concentration in microenvironment j , t_{ij} is the aggregate time that person i spends in microenvironment j ; and J is the total number of microenvironments that person i moves through during the specified time period (Duan, 1982).

The concept of a time-weighted integrated exposure is illustrated in Table 9. It shows that a person passing through different microenvironments during a 24-hour period will be exposed to different concentrations of carbon monoxide (CO).

It should be noted, however, that the concentration of an air pollutant in a microenvironment may not be homogeneous, but may change with the time a person spends there, for instance at home, because of smoking, opening and closing of windows etc. In addition, individuals sensitive to tobacco smoke are likely to leave a room where people smoke, or may avoid such microenvironments entirely. It may not be clear which microenvironments to study in order to include all significant sources of exposure.

Geographic Information Systems (GIS)

Geographic information systems (GIS) have increasingly been used for exposure assessment in epidemiological studies during recent years. A GIS can be described as a method of analysing spatial data. All spatial data can be geocoded, that is described by x and y co-ordinates in a geographical co-ordinate system. A modern GIS is computerised and uses database techniques. Thus, in a GIS, different data in databases with geocoded observations can be analysed and visualised. Maps are essential parts in a GIS and may be used for both input and output of data.

An early example of how GIS techniques may be used for environmental health studies is the famous London cholera study by Dr John Snow in the 1850s. Although John Snow did not have access to modern computers, he plotted cholera cases on a map of Soho and found that there was a clustering of cases around one of the water pumps. When the pump was closed, the number of cholera cases decreased dramatically and John Snow deduced that contaminated water from that particular pump was the cause of the cholera epidemic in Soho. A GIS was very useful in this example, since it was clear that the inhabitants of Soho drank water from the local pumps and since the latency time between intake of contaminated water and the outbreak of cholera was short.

Sometimes the use of GIS has been less well considered. A common mistake is the neglecting of the time factor, in that GIS is used to assess present exposure, which is then linked to present disease prevalence, even if the disease under study has a long latency period, like most chronic diseases. Using GIS for exposure assessment for diseases with short latency periods should be more relevant, but selection problems may lead to grossly erroneous results. For example, some studies have found a negative relationship between air pollution and asthma. However, asthmatic persons may have left the study area due to the air pollution and such a migration out of the area might well explain the apparent negative association.

As emphasised in previous chapters, a key issue in exposure assessment is the definition of exposure; a person is exposed only if there has been a contact between the agent under study and a body surface. Several GIS exposure assessment study designs have ignored this, in particular regarding water pollution. In contrast

to ambient air, which we all breathe, it is not obvious that water pollution results in exposure. Even if it can be established that water pollutants are present at the tap, exposure may not occur if the tap water is not used for drinking.

GIS was used to study lung cancer incidence in Stockholm (Nyberg et al, 2000). Lung cancer incidence is increased in urban areas, and it is well established that smoking is the most important risk factor, but although smoking is more common in cities this does not fully explain the excess risk. Other important risk factors are domestic radon exposure and environmental tobacco smoke. There has also been much discussion about the role of ambient air pollution in the causation of lung cancer. In particular, motor vehicle exhausts may play an important role as pollutants of ambient air and as occupational exposure among professional drivers. Therefore an epidemiological case-control study was carried out, one aim being to evaluate the importance of air pollution for the development of lung cancer. In this study, 1,000 cases of lung cancer in men aged 40 to 75 diagnosed between 1985 and 1990 were identified in the regional cancer registry and 3,000 controls were selected from the general population.

Information on individual exposure was collected with a postal questionnaire, including questions on dwellings from 1950 and onwards. The home addresses were then transformed into geographical co-ordinates using GIS computer software in conjunction with a regional geographical database. The validity of the geographical co-ordinates was assessed by a visual graphical method and by comparison with another GIS method of assigning co-ordinates.

Exposure to air pollution was estimated from emission databases by dispersion modelling of SO₂, NO₂ and NO_x. The air pollution data were then linked to the individual address co-ordinates for the relevant time intervals, yielding cumulative exposures for each of the three air pollution components.

The main finding of the study was that average traffic-related NO₂ exposure (over a 30 year period) was associated with an increased lung cancer risk, after adjustment had been made for smoking, socioeconomic status, residential radon and occupational exposures (Nyberg et al, 2000).

As noted in the section on ecological studies (Chapter 3, p. 42), GIS is a useful tool in the analysis of routinely collected data. Several countries and the WHO have produced large-scale maps of certain diseases, in particular cancers, for many years. The interested reader should consult the IARC (International Agency for Research on Cancer) web-site (<http://www.iarc.fr>) to study the GLOBOCAN cancer maps, which give a good overview of the distribution of cancers worldwide. Another web-site worth visiting belongs to the US National Cancer Institute (<http://www.nci.gov>) and shows US cancer maps. GIS has also been increasingly used for mapping of diseases at a small area scale, in particular in the UK.

For further studies of Geographical Epidemiology, the reader is referred to Elliott et al, 2000.

After reading this chapter you will:

- Be aware of the philosophy of quality assurance and quality control
- Be familiar with key concepts used in analytical quality control
- Be able to recognise sources of errors in analytical quality control and their consequences

Definitions and scope of quality assurance and control

Quality assurance (QA) programmes are critical components of all exposure assessment studies. Quality assurance should be integrated in all stages before, during and after collection of data. Quality assurance refers to all procedures used to ensure data reliability. It covers the utilisation of scientifically and technically sound practices for the study design, the collection, transport and storage of samples, the laboratory analysis, as well as the recording, reporting and interpretation of results (WHO, 1984). It also refers to training and management designed to improve the reliability of the data produced. Auditing procedures should be used to control the quality of all steps taken during a study, including the recording and reporting of data. Although non-quantitative, such procedures will generally make the operator aware of possible errors. In order to ensure reliable exposure data, quality assurance programmes should always be implemented together with the exposure assessment study.

Quality control (QC) refers more specifically to the overall system of technical activities aiming to measure and control the quality of the study results. The internal quality control (IQC) is a set of procedures used by the staff for continuously assessing results as they are produced in order to decide whether they are reliable enough to be released. The external quality control (EQC) is a system for objective checking by an external agency of the work performed.

Pre-analytical quality control

Pre-analytical quality control refers to all steps to be taken to ensure correct sampling, that is to get representative samples and to avoid contamination of samples. Strategies for sample collection, transport and storage should be decided on prior to study start. A sampling protocol should be prepared. Careful training of all personnel involved in the study, as well as information to participating subjects, is also needed.

A suitable number of all equipment and containers used for sampling and storage of samples should be tested for possible contamination (for example, blood collecting tubes should be proved to be lead-free in a blood lead study). Instruments and equipment for sampling should be routinely calibrated and checked for deviations (for example, a personal air sampler should be checked to keep a constant flow rate throughout the sampling period).

Samples should be handled and stored at a temperature that keeps the sample intact prior to analysis. All samples should be properly labelled and registered.

Analytical quality control

The analytical quality control refers to all activities aiming at measuring and control the quality of the analytical results. It should include both internal and external quality control. The internal QC includes analyses of samples with known concentrations of the substance to be measured. Commercially available reference materials may be suitable for this, but usually only a few concentrations are available, especially in the low concentration range. The purpose of the internal QC is to calibrate the analytical equipment and to check the analytical performance. An external quality control programme should preferably evaluate the accuracy and precision of the analytical methods used. If this is not possible, the results obtained with the routine method may be compared with those of a reference method, or another method using different analytical principles, preferably at another laboratory. Inter-laboratory comparisons of analytical results from analyses of the same sample are also useful.

Analytical quality control samples

Analytical quality control samples should consist of the same medium as the one under study and the concentrations should be in the same range as in the collected samples. It has been shown that a satisfactory analytical result for one concentration in one type of medium does not guarantee satisfactory results for another concentration in another type of medium. However, very few QC samples with useful concentrations are commercially available and therefore such samples may need to be produced for a given project. Ideally a relatively large homogeneous quantity of material should be made available, so that the same batch can be used throughout the study period. A sufficient number of samples should be analysed by several laboratories to obtain the best possible reference values. These reference values are later used for comparison with the analytical results from other laboratories on samples of the same material. By the use of a set of QC samples, covering a range of concentrations, analytical performance can be evaluated by linear regression analysis of obtained analytical results versus reference (or expected) values (Figures 22 and 23, p. 110 and 112). This approach was taken in the UNEP/WHO HEAL study on lead and cadmium (Vahter et al, 1991). Quality control samples for lead and cadmium in blood, faeces, air filters, dust and diets were prepared since no suitable reference samples were commercially available (Lind et al, 1988; Jorhem and Slorach, 1988). The QC samples were used as EQC samples in the participating laboratories in China, Japan, Sweden, and former Yugoslavia. The results of the analytical performance improved during the analytical training phase, and during the monitoring phase of the study all laboratories met the analytical quality criteria.



Some sources of reference materials with general coverage:

- BCR, Community Bureau of Reference (CEC);
Contacts Address: 303 Rue de la Loi, 200 B-1049, Bruxelles, Belgium.
Fax: +32 2 235 8072
- IAEA, International Atomic Energy Agency; Contacts Address: Department of Technical Cooperation, International Atomic Energy Agency, Wagramerstrasse 5, P.O. Box 100 A-1400 Vienna, Austria. Phone: 43 1 2060 (plus 5-digit extension)
Fax: +43 1 20607
- NIES, National Institute for Environmental Studies, 16-2, Onogava, Tsukuba, Ibaraki, Japan
- NIST, National Institute of Standards and Technology. Mail stop 2310, Gaithersburg, MD 20899 2310, USA.
Fax: 301 926 0416

These and other suppliers can be found on the Internet.

Reference materials

The primary uses of reference materials are to check the calibration, to document traceability and for performance control. It is necessary to differentiate between reference materials, the contents of which are known and well-defined, and intercomparison materials, for which the content is not known in advance. A certificate stating the value and a confidence interval accompanies certified reference materials. Ideally, the reference material should be as close as possible in chemical composition to that of the sample and should also contain the analyte at about the same concentration as is present in the sample. In many cases, suitable reference materials do not exist, but even if an exact match cannot be obtained, the use of the closest available is better than using none. A survey of organisations and laboratories manufacturing, supplying or using reference materials for environmental measurements has been published by UNEP (1992). A survey of commercially available reference materials has been prepared by IAEA in co-operation with UNEP (IAEA, 1995; 1996). A search for analytical (certified) reference materials on the Internet may be useful, to find organisations and producers of suitable materials. There is also a large searchable database for certified reference materials, COMAR (<http://www.bam.de/comar>), with more than 200 producers of reference materials throughout the world. Examples of suppliers of reference materials are given in Box 14.

Commercial external quality assessment schemes



There are several external quality assessment schemes (EQAS) commercially available (Box 15). These schemes cover a broad range of analytes (trace elements and organic compounds) and matrices (blood, serum, urine), and have developed different procedures for the evaluation of laboratory performance. An evaluation of twelve EQAS in occupational and environmental laboratory medicine in nine European countries has been published (Taylor et al, 1996). More information can be found on the Internet.

Record-keeping and data validation

Detailed records, with dates, should be kept on the introduction of new batches of supplies, such as filters, reagents, sample containers, plastic-ware and pipettes. Likewise, changes in instrumentation or personnel should be recorded. Afterwards, when analysing the reasons for changed analytical performance, this kind of thorough record-keeping is of utmost importance.

Sometimes changes in the analytical performance are not abrupt but take place gradually (“drift”). Such drifts are difficult to perceive from a single central result, but may become evident with time if the results of control samples are graphically displayed. In a control chart, values of whatever is being measured are plotted in time sequence. The chart graphically displays the fluctuations of the measured values. A variety of control charts are in use, for example, the CUSUM chart and the Shewhart chart (Figure 20, p. 107).

Some examples of EQAS extending their services world-wide

- Danish External Quality Assessment Scheme (DEQAS), Danish National Institute of Occupational Health, Copenhagen, Denmark
- FIOH external quality assurance scheme for organic solvent metabolites, Finnish Institute of Occupational Health (FIOH), Biomonitoring Laboratory, Helsinki, Finland
- German external quality assessment scheme in occupational and environmental medicine, German Society for Occupational and Environmental Medicine, Erlangen, Germany
- Guildford Trace Element Quality Assessment Scheme, Robens Institute of Industrial and Environmental Health, University of Surrey, Guildford, UK
- Interlaboratory Comparison Program for Trace Elements in Biological Fluids, Toxicology Centre, Quebec, Canada

Data validation usually consists of two parts:

- Data entry procedures
- Acceptance procedures

There is always a risk of introducing errors while transcribing data into computer files. These are so-called clerical or human errors that may not only involve numerical errors but also formatting errors, identification errors, etc., which can lead to a serious bias in the analysis of data. Data should therefore be checked either visually or by use of computerised procedures flagging potentially erroneous data.

Acceptance procedures are designed to compare the reported data against specified criteria in order to judge the reasonableness of the reported values. Acceptance procedures identify various types of anomalies in the data including impossible values, individual and multiple outliers, and entire subsets of incorrect data.

Quality control information should always be published together with the exposure data in order to make possible evaluation of the validity and reliability of the corresponding exposure data, and to ensure comparability of data. Also, re-evaluation of data can be performed at a future point.

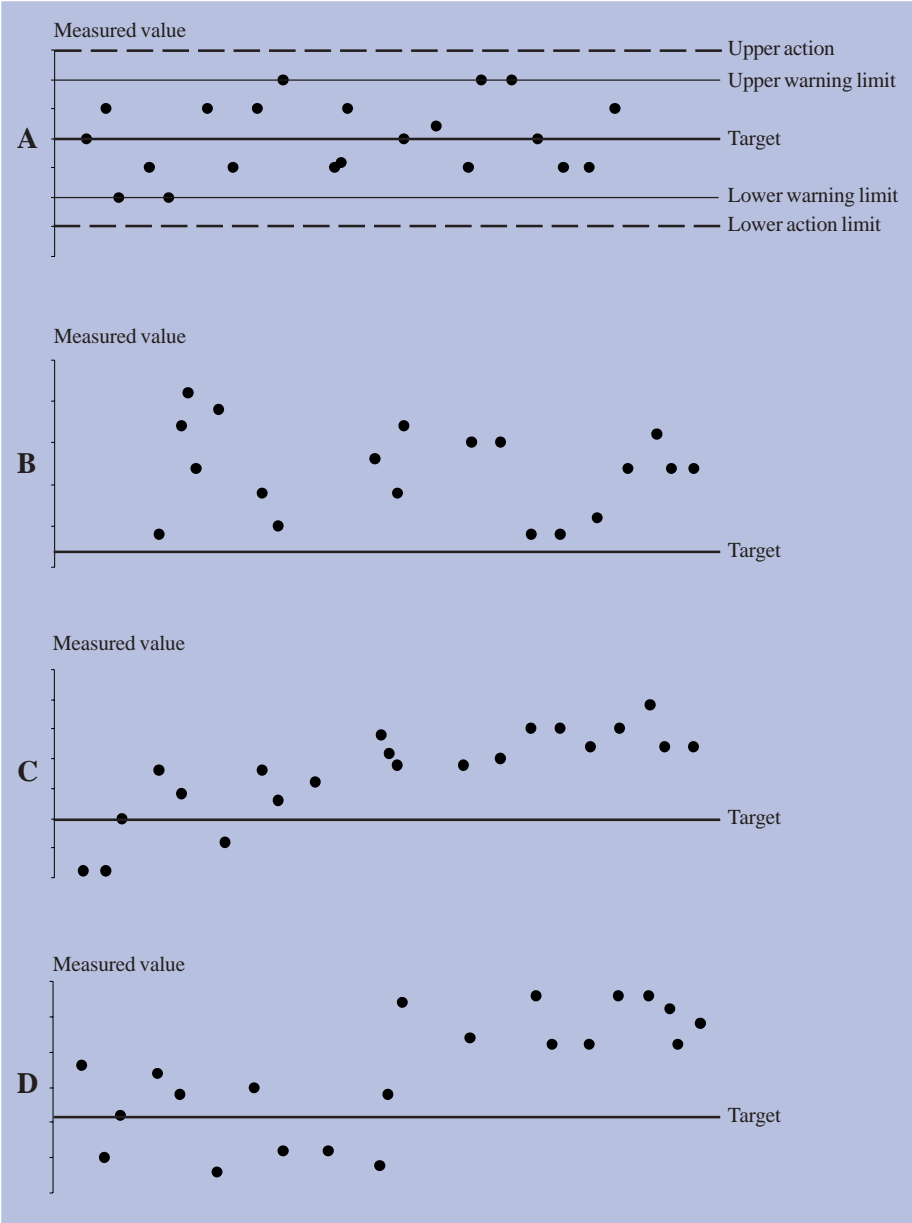


Figure 20. Example of the Shewhart chart. A) Data in control about the target value. B) Data offset from the target value. C) Drifting data. D) Data with a steep change (Prichard, 1995).

Sources of variation in analytical results

Concentrations of xenobiotics measured in exposure assessment studies involving the general population are often very low. Advanced analytical techniques as well as sensitive methods for detection of systematic errors in the analytical results are required in order to make possible detection of the small deviations from baseline exposure that may cause health effects.

A quantitative measurement is always an approximation of a true value. Many factors contribute to this deviation. The analytical equipment may not be perfect, the analytical method may not be specific or sensitive enough, and biases may not be identified and corrected for. An exposure assessment study should therefore always report the uncertainty of the exposure estimates.

When the concentration of a pollutant is determined repeatedly in the same laboratory, a certain scatter of the measured quantities is always seen. Analyses of the same sample by different laboratories usually show even greater variation. In both cases, the variations incorporate a component of analytical variation as well as changes that may take place during sample collection, preparation and storage (UNEP/WHO, 1986).

Collection of samples

A major problem in sampling is contamination. The highly sensitive analytical methods used today permit analyses of small sample sizes, and the amounts of pollutants are often very low in each sample. The risk of contamination is particularly high for substances that are ubiquitous in the environment or substances that are present in materials and tools that can come into contact with the sample.

Handling and storage of samples

The samples must be handled and stored in such a way that the level of the substance to be analysed remains stable. The processes that are most likely to decrease sample stability are precipitation, chemical deterioration, surface absorption and evaporation of the analyte. Another factor that might be important is changes in the matrix, leading to changes in the recovery of the analyte.

Gross errors

These include sample mix-up, calculation errors, and sample/standard dilution errors. Gross errors, particularly if they lead to exceptionally high or low results (so-called outliers), are difficult to deal with and the procedure should include ways and means for detecting and accepting or rejecting them.

Analytical variation

Analytical variation may be divided into two major categories: *accuracy* which refers to the agreement between the amount of analyte measured and the amount actually present, and *precision* which refers to the uniformity of results of replicate analyses, irrespective of the true concentration of the analyte, under a given set of conditions (Figure 21). The precision or reliability of an analysis may vary depending on many factors, for example the skill and experience of the analyst, the purity of the chemicals, the quality of measuring devices and the time interval between replicate analyses.

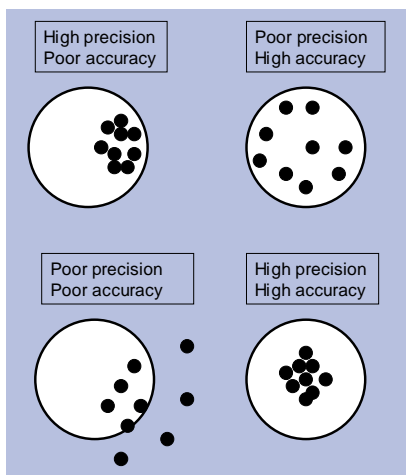


Figure 21. Graphical illustration of accuracy and precision.

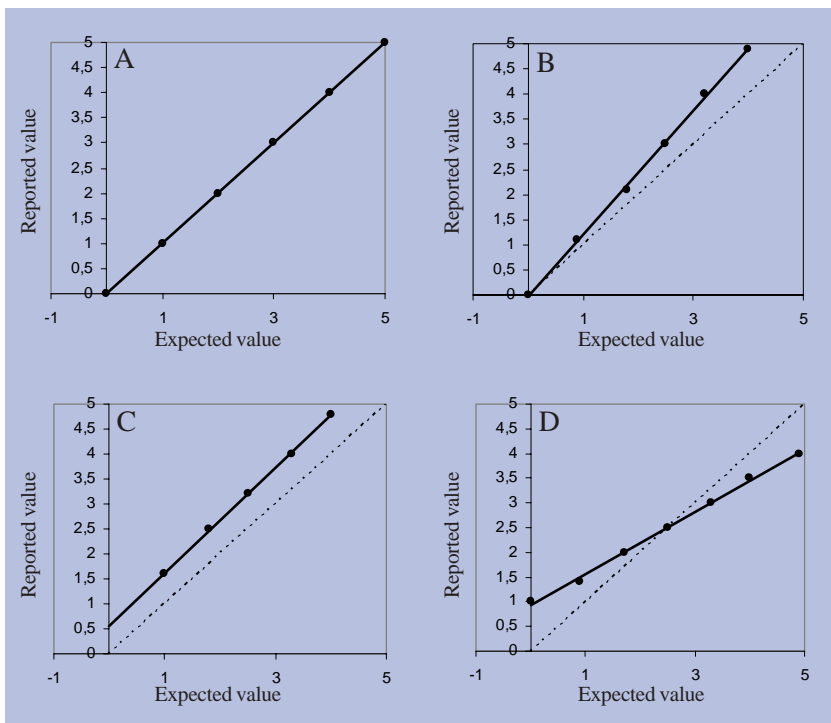


Figure 22. Illustration of the ideal case and various types of bias (for explanation see text; UNEP/WHO, 1986). The dotted line illustrates the ideal line $y=x$.

Accuracy or validity of an analysis is primarily determined by the specificity of the method and the analytical recovery. In addition, errors in calibration decrease accuracy. Low accuracy of an analysis indicates a bias.

Figure 22.A illustrates the ideal case where the reported values correspond exactly to the expected (or reference) values. However, all analytical procedures are subject to a variety of analytical inaccuracies or biases. Figure 22.B shows the effects of a proportional bias in which the reported values are higher than the expected values. The bias is called proportional because the amount of bias increases in direct proportion to the concentration of analyte in the specimen. Figure 22.C illustrates the effect of a constant bias, in which each of the reported values are higher than the expected values by a constant amount, at all

concentrations of the analyte. The biases shown in Figures 22.B and C are positive biases, because the reported values are greater than the expected values. Negative biases may also occur, and the reported values may fall along a curve rather than a straight line. Figures 22.B and C illustrate the two major classes of biases that affect the accuracy of analyses. Many analytical procedures are subject to either constant or proportional biases, or to both. Figure 22.D illustrates how combined constant and proportional biases may affect the correlation of reported and expected values. It is worth noting that when combined biases are present, there is frequently one concentration at which the reported value corresponds exactly to the expected value. This phenomenon is commonly observed and must be considered when interpreting quality control data. It is therefore recommended that reference samples cover the range of expected measurement values.

The effects of random variation on analyses are illustrated in Figure 23 (p. 112). It shows how a laboratory's results may be fitted to an operational line with certain limits of variability. Figure 23.A illustrates a variability that increases in proportion to the mean analyte concentration, while Figure 23.B illustrates a variability that is constant at all concentrations of the analyte.

Knowledge of the kinds of bias and random variability that affect an analytical system is helpful in identifying their causes. For example, proportional limits of variability are commonly caused by imprecision in volumetric dispensing of the sample. An automatic pipette is a mechanical device and as such there may be a certain amount of play in the operation of its parts, which may increase as the parts become worn. Variation in the amount of samples measured by such a pipette will introduce variation in the analytical results proportional to the analyte concentration of the specimen. This will cause proportional variability, as shown in Figure 23.A. Similarly, constant limits of variability are commonly observed in analytical procedures that are influenced by the turbidity of the specimen. Sample turbidity is usually independent of analyte concentration, but may vary between specimens, causing results to be distributed between constant limits (Figure 23.B). Thus, knowledge of how various sources of analytical bias and variability affect the accuracy and precision of the operational line can be most helpful in identifying and in correcting analytical problems as they arise.

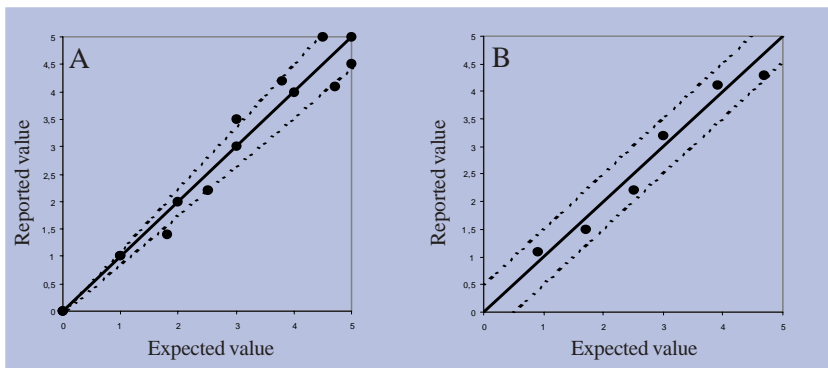


Figure 23. Illustration of random analytical variability (for explanation see text; UNEP/WHO, 1986).

Analytical method selection

A chemical compound can usually be analysed by a variety of different methods. Some methods emphasise the quality of analysis, while others are directed mainly towards practicality and low cost. However, even the best method may give incorrect results if improperly used. Methods are customarily classified according to their main use in the analytical field into definitive, reference and routine methods.

The best approximation of the true value obtained by analysis is the definitive value, that is the result obtained by the definitive method. The definitive method is generally not considered practicable for daily laboratory use. It is generally used to back up reference methods. The purpose of a reference method is to serve as a basis for the determination of the accuracy of routine methods. Routine methods are those used regularly in the laboratory. They are usually not as precise and accurate as reference or definitive methods. Their use is justified, however, because the definitive and reference methods are too cumbersome and expensive. For every routine method used, precision and bias relating to the method should be known. It should be pointed out, however, that additional bias might be introduced as a result of the application of the method.

Quantitative estimation of analytical precision

Statistical analysis of environmental samples collected simultaneously in space and time can be used to estimate the precision of a measurement method. Such samples are often referred to as duplicates and are collected in pairs. The difference in the measurement parameter (e.g. concentration) between a duplicate pair is indicative of the precision of the collection and analysis methodology. Descriptive statistics generated from a set of differences between duplicate samples can be used to characterise the average degree of precision, as well as the variability in precision.

Consider a hypothetical study of respirable suspended particulate matter (RSPM) in outdoor air where 20 duplicate pairs of 24-hr average measurements were made. Assume the 24-hr average concentration among the 40 measurements was $50 \mu\text{g}/\text{m}^3$. Further assume that the distribution of differences between the 20 pairs of duplicate samples was normally distributed with a mean and standard deviation of 5 and $1 \mu\text{g}/\text{m}^3$, respectively. On average, then, a single measurement can be expected to be within $5 \mu\text{g}/\text{m}^3$ of the actual concentration. A single measurement can be expected to be within approximately 3 to $7 \mu\text{g}/\text{m}^3$ of the true concentration 95 % of the time, i.e. within ± 2 standard deviations of the average difference.

For a probability distribution, the coefficient of variation (CV) is defined as the ratio of the standard deviation to the point estimate of the mean ($1/5$). In this way, the coefficient of variation error describes the degree of dispersion of a dataset relative to a measure of its central tendency. The coefficient of variation provides a quantitative estimate of the relative degree of variability among the observations in a dataset. Using data from the hypothetical example described above, the coefficient of variation among the pairs of duplicate samples is $1/5=0.2$. Thus, on average, a single measurement can be expected to be within 20 % of the actual concentration.

Intentionally blank

After reading this chapter you will:

- Be familiar with some of the basic methods for describing exposure data
- Be able to organise, illustrate and present data
- Be aware of common methods of statistical analysis
- Be guided to further statistical methods

This chapter describes briefly statistics relevant to various aspects of data analysis and presentation. It is, however, not within the scope of this text to cover in detail all statistical aspects relevant for exposure assessment. The reader wishing to design or participate in exposure assessment studies should study the relevant statistics in more depth.

Choice of statistical methods

Data could be measured by different types of scales. Data measured by numerical values (e.g. concentration of lead in blood, $\mu\text{g}/\text{litre}$) are called nominal data. Data measured by order or rank (e.g. distance from plant: within 0.5 km, 0.5-1 km, >1 km) are called ordinal data, and data measured by proportions or number of observations in categories (e.g. male versus female) are called interval data. Commonly, an exposure assessment study produces questionnaire data, including activity logs, food consumption records, place of residence, etc., and pollutant concentrations in various media such as inhaled air, indoor residential air, food, water, exhaled breath, mother's milk, blood, urine, etc. When data have been collected, all the information gathered should be analysed in a scientifically sound manner, and presented to whom it may concern. The presentation of the data should be as clear as possible.

Statistical methods are used to describe the data and to aid understanding of the basic characteristics of exposure and its determinants. Descriptive statistics include measures of central tendency such as arithmetic mean (average) or median, and measures of dispersion such as standard deviation and percentiles. Statistical methods are also used to analyse the data in such a way as to compare two or more groups for significant differences, predict a trend, explore associations between various parameters measured, and for hypothesis testing. Furthermore, statistical inference allows generalisations of the observations derived from a sample to a wider population from which the sample was drawn.

In data analysis procedures, it is necessary to take into account the distribution of the data. Environmental exposure data are most often normally or log-normally distributed, the latter being most prevalent. A logarithmic transformation of log-normal data produces a normal distribution, which can be further treated with statistical procedures applicable to normal distributions (Figure 24). These are called parametric methods.

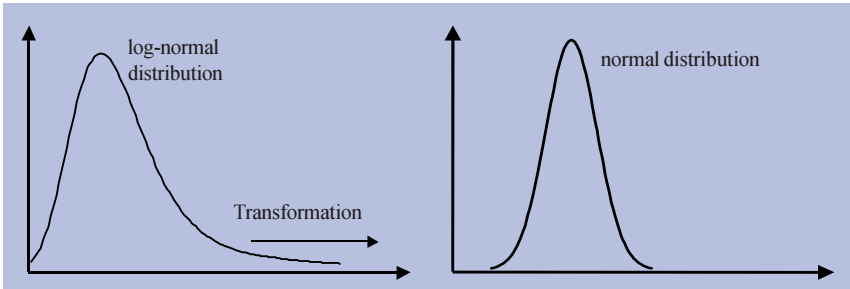


Figure 24. A logarithmic transformation of data can produce a normal distribution.

Many exposure-related datasets do not fit this description, however. One reason for this is that the data may not be normally distributed or cannot be transformed so that they are approximately normal. Non-parametric statistical analysis methods can be used to analyse data with these characteristics. A more common reason is that although the underlying distribution of the population from which the sample is drawn may be approximately normal or log-normal, the number of samples is too few to allow the nature of the underlying distribution to become apparent.

Sample sizes are often small in exposure studies because of logistical difficulties in collecting samples and the expense of collecting and analysing the samples. It is therefore crucial to perform sample size and power calculations during the study design phase in order to be able to fulfil the objectives of the study (Chapter 4, p. 55).

Widely available statistical software for personal computers can be used to perform data processing and necessary calculations. One example of such packages is the statistical free-ware programme EPIINFO developed for and distributed by WHO. However, sometimes it is recommended that special-purpose statistical software should be used to analyse data. It is wise to consult statistical expertise if the investigator lacks the necessary knowledge to be able to choose the appropriate statistical method for the analyses.

Description of data

Descriptive statistics summarise data in a simple manner to discern key points about the information collected. We typically assume that the data collected are a sample from a larger population of possible measurements and that the sample is representative of the population. The sample consists of the individual observations from the study population, with multiple variables or covariates recorded for each observation. Univariate methods examine the distribution of a single variable. Multivariate methods describe relationships among two or more variables. That is, if we consider a single observation and know the value of one variable, multivariate methods indicate what we can infer about the other variables. Both numerical and graphical techniques may be used to characterise the sample and any relevant subset, and to obtain preliminary results from the study.

Data can be presented in various forms, including frequency tables, histograms, bar charts, cross-tabulations, pie charts and box plots. For most questionnaire data, tabulations of the percentages that belong to various categories of interest will be appropriate. Unweighted tabulations that simply describe the individuals and dwellings in the sample may also be of interest. Examples include demographic characteristics of the study participants, types of housing, and variables potentially related to environmental measurements.

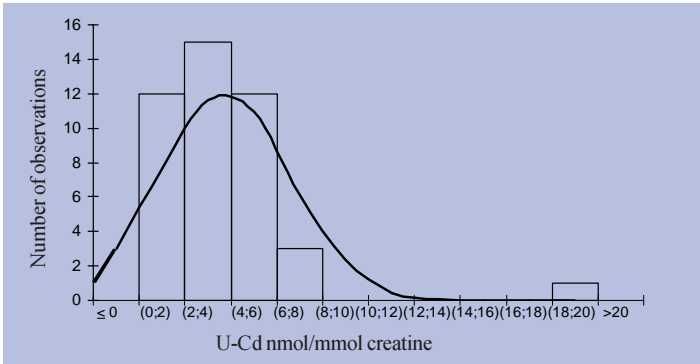


Figure 25. A histogram presentation of urinary cadmium concentrations in a group of cadmium exposed workers. The smooth curve approximates the distribution (data from Järup and Elinder, 1994)

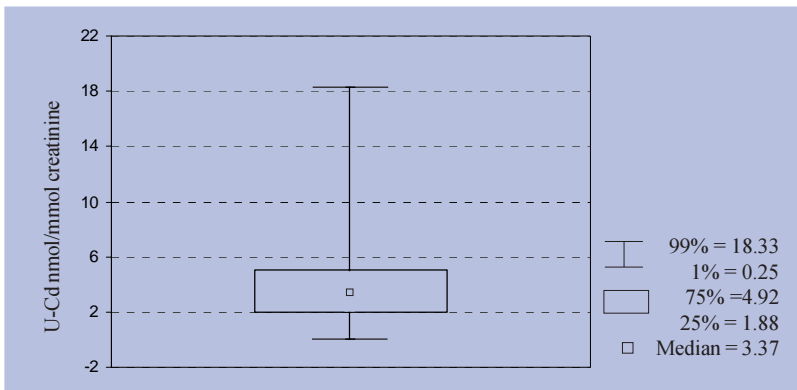


Figure 26. A box plot presentation of the same data presented in figure 25.

Displaying both the arithmetic and the geometric means (or medians) is a useful way of describing the distribution of the data. A large difference between the arithmetic mean and the median implies that there is a skewed distribution of exposure measurements. It should be noted, however, that this does not imply that the measurements behave like a log-normal probability distribution.

Standard measures of dispersion include the sample variance (s^2), the standard deviation (SD), percentiles, and the range (min, max). These measures describe the spread of the observations. Measures of dispersion are useful for describing the degree of variability of a given measure among the members of a study population. Figure 25 shows a histogram of urinary cadmium concentrations in a group of cadmium exposed workers. The figure also includes a smooth curve approximating the distribution presented. Figure 26 shows an example of a box plot presentation of the same data. The design of the box could be chosen to suit the need of the investigator; in this case it was considered appropriate to show the median, the 1, 25, 75 and the 99 percentiles. The median represents the value in the middle of the distribution and, for example, the 75th percentile is the measure which 75% of the distribution is below.

Table 10 shows an example of analytical results from a study of cadmium exposure in a population of Stockholm women.

Table 10. Example of presentation of results (exposure and effect estimates) from a study of cadmium exposed women in Stockholm, Sweden, showing the means and variability. SD = Standard deviation. NAG=N-acetyl-β-D-glucosaminidase.

Analysis, urine	Arithm. mean	Arithm. SD	Min	Max	Median	Geom. mean	75 th percentile	90 th percentile
Cadmium ¹	0.59	0.31	0.15	1.71	0.53	0.52	0.76	0.99
Density ²	1.02	0.01	1.00	1.03	1.02	1.02	1.020	1.024
Creatinine ³	7.27	4.52	1.20	21.32	6.44	6.07	8.78	14.01
Calcium ⁴	3.47	2.73	0.20	13.0	2.70	2.56	4.60	7.40
NAG ⁵	2.99	1.87	0.40	10.9	2.60	2.53	3.80	5.40

¹nmol/mmol creatinine, ²g/cm³, ³mmol/l, ⁴mg/l, ⁵U/l

Data analysis

Regression analysis and analysis of variance techniques are useful for analysing the relationships between exposure and explanatory variables. Analysis of variance (ANOVA) is a technique for assessing how several nominal independent variables affect a continuous dependent variable and is usually concerned with comparisons involving several group means. Regression and ANOVA models are closely related and can be analysed within the same framework. The major difference is that for ANOVA, all the independent variables are treated as being nominal; while for regression analysis, any mixture of measurement scales (nominal, ordinal, or interval) is allowable for the independent variables. Estimation for both ANOVA and linear regression models consists of obtaining point estimates for the parameters that describe the mean exposure under a certain set of conditions. Part of the estimation procedure is to determine how well the model fits. The first diagnostic is to examine the residual error (residual). A residual is simply the difference between the exposure estimated by the model and the actual exposure. By examining the residuals, one can determine for what ranges of actual exposures or conditions the model does not fit well, and use this to decide how to adjust the model.

A regression model is used to evaluate the relationship of one (simple regression analysis) or more (multiple regression analysis) independent variables X_1, X_2, \dots, X_k to a single, continuous dependent variable Y . It is often used in exposure assessment to characterise the relationship between the dependent and independent variables (continuous and discrete) by determining the extent, direction, and strength of the association (correlation). Examples of simple regression analyses are given in Figures 22 and 23 (Chapter 6, p. 110, p.112). For example, in the particle total exposure assessment methodology (PTEAM) study, indoor $PM_{2.5}$ concentrations (Y) were regressed against outdoor air concentrations (X_1), smoking rates (X_2), cooking durations (X_3), air exchange rates (X_4), and house volumes (X_5) to determine the major factors affecting indoor $PM_{2.5}$ concentrations (Ozkaynak et al, 1996).

Sensitivity analysis

Throughout the history of modern epidemiology, efforts have been made to quantify the errors in (relative) risk due to sampling inaccuracy. Several methods have been designed to compute confidence intervals as a measurement of the risk estimate uncertainty imposed by the sampling procedure. The confidence interval thus mirrors the uncertainty in the risk estimate due to sample size. Much less attention has been given to the errors in risk estimates due to inaccurate assessment of exposure, although numerous studies have been published dealing with the consequences of the mis-classification of data resulting from imprecise measurements. Most epidemiological studies discuss the mis-classification problem, but in many studies it would have been possible to estimate the magnitude of the measurement errors involved and thus obtain more accurate estimates of the impact of the resulting mis-classification.

In occupational and environmental epidemiological studies the independent variables, often collected from questionnaires, are usually estimated with large errors. One way of estimating the impact of such errors is to perform a basic sensitivity analysis, checking how changes in the data estimates will influence the risk estimates (Box 17, p. 122).



An example of a basic sensitivity analysis

An example of a basic sensitivity analysis in a study where exposure was assessed retrospectively is taken from the occupational cohort study of arsenic exposure and lung cancer in copper smelter workers (for a detailed description of the study - see Chapter 9, p. 151). Arsenic exposure was estimated through a thorough assessment of industrial hygiene data made by an experienced occupational hygienist. The data included historical documents such as work safety committee reports and internal company papers concerning the work environment at the smelter.

Early air measurements had revealed very high arsenic concentrations in the 1940s, with an average of almost 1 mg/m³. Regular monitoring of the workroom air was carried out from the middle of the 1950s. These detailed data made it possible to compute individual cumulative arsenic exposure estimates. Using these estimates and the regional reference data, Standard Mortality Ratios (SMR) were computed for different exposure categories. It is reasonable to assume rather large errors in the early exposure data, particularly before 1940 when no air measurements were available. The exposure data from that period were estimated from other sources, such as production figures, sick leave data and interviews with workers and management. The estimated air concentrations of arsenic between 1940 and 1950 depended heavily on rather few measurements that most likely had large standard deviations. To assess the influence of errors in these early data, new sets of SMRs, assuming “worst case” deviations in the exposure data, were computed. A large overestimation of the early exposure data was assumed. The results are shown in Table 11. In spite of the large errors assumed, the revised SMR₁ was similar to the original SMR₀ in three of the four exposure categories, indicating a robustness in the data. The increased SMR₁ in the highest exposure category is the expected result of a large overestimation of the cumulative exposure, due to errors in the early exposure data.

Table 11. Standard Mortality Ratios (SMR) computed for different exposure categories. SMR₀ was computed using the original exposure data. SMR₁ was computed using exposures prior to 1940 multiplied by 0.5, and exposures between 1940 and 1950, multiplied by 0.75. CI = confidence interval (from Järup, 1992).

Exposure category mg/m ³ × years	SMR ₀	95 % CI	SMR ₁
< 0.25	272	145 - 465	284
0.25 - < 15	301	218 - 404	338
15 - ≤ 100	500	348 - 695	531
> 100	1151	595 - 2011	2011

After reading this chapter you will:

- Be able to recognise the importance of ethical issues in exposure assessment studies
- Be aware of possible ethical conflicts when designing a study
- Be aware that most exposure assessment studies should be approved by an ethics committee

Ethical questions should be raised by every scientist involved in exposure assessment studies. Most countries, as well as scientific journal editors, demand that studies involving humans should be approved by an ethics committee. It should be an independent body that review research proposals on humans with regards to ethics of the work proposed. Environmental epidemiologists and exposure assessors should assess their practice from an overall perspective that includes concern for the integrity and sustainability of all regional, national and global life-support systems. Public health interests should always take precedence when potential conflicts arise. Four principles of ethics exist: respect for autonomy, beneficence, non-maleficence, and social justice. The following ethical considerations should be borne in mind when an exposure assessment study is planned:

- When practical, informed consent from study participants should be obtained (Box 18). This is usually also a demand from the ethics committee before approving the study protocol. It is the responsibility of the researcher to protect the integrity of the individuals and to keep the data confidential
- Financial compensation to study participants should only cover expenses to avoid bias
- Best scientific standards should be employed (as in all scientific research)
- Study results should be reported to decision makers and to the public, stating also the level of scientific uncertainty involved
- More research should be conducted among “understudied” population groups

In recent years, environmental research professionals have expressed a growing interest in the ethical issues. The International Society for Environmental Epidemiology (ISEE) has together with the WHO (through their Global Environmental Epidemiology Network, GEENET) conducted a survey among scientists involved in epidemiological studies to evaluate the ethical views of the scientific community. A very low response rate (30 % among ISEE members and only 19 % among the GEENET members) may be an indicator of a rather low interest in the ethical issues. Nevertheless, certain recommendations were proposed to promote ethical discussions among environmental epidemiologists. It was suggested that core values for environmental epidemiologists be defined and that a set of ethics guidelines be developed (Soskolne and Light, 1996, WHO 1996b). It was also suggested that ethic issues should be discussed at professional meetings, which was implemented on a trial basis at the ISEE yearly conference in Edmonton 1996. Since then, sessions on ethical issues have been included in the ISEE annual meetings.

The emerging use of biomarkers for genetic susceptibility may reveal several new associations between exposure and disease, where the risk for disease is greatly increased in a particularly susceptible subgroup of the population. How should this new information be used? Ideally, the risk estimates uncovered may be used to set lower standards for harmful agents to protect the most susceptible individuals. The information may, however, also be used to exclude the susceptible persons from the hazardous environment. Screening for genetic susceptibility may, for example, be used to select individuals to particularly dangerous jobs in the chemical industry, where exposure to harmful agents may occur. Furthermore, the information of such a susceptibility to the individual may induce concern, which may be more harmful than the susceptibility itself.

Revealing research findings to the public often poses an ethical dilemma. On the one hand it is desirable to communicate findings indicating for example potential associations between environmental factors and disease; on the other hand such associations may be less well founded and cause unnecessary anxiety. Thus, dissemination of study results should be carefully planned and preferably involve the general public as well as the scientific community.

Another ethical conflict is the possibility of biased study designs that may result from economic pressure or poor science. In a survey among risk assessors it was found that 30 % of the respondents had observed such biased study designs. Other observations were plagiarism (20 %) and fabrication of data (10 %). That the two latter findings constitute unethical behaviour is probably unquestioned by most scientists; nevertheless both plagiarism and fabrication of data seem to occur in a number of cases.

A number of questions have arisen about the extent to which specimens collected for one purpose can be used for related or for distinctly different research (Schulte and Sweeney, 1995). When subjects are recruited, the investigator should inform them of the study purpose and study details, the risks and benefits of participation, and describe any possible use of data in the future. If unplanned use of specimens arises, does the investigator have to obtain informed consent from the participant to use their sample? This is still an open question. The banking and use of specimens also raises the question of ownership of specimens.

Informed consent

- Each participant must be thoroughly informed about the objectives of the study, the risks and the benefits
- Participants must not be pressured in any way to participate
- It should be possible to withdraw at any point without prejudice

Intentionally blank

Introduction to field examples

Exposure assessment studies are conducted for various reasons. In this chapter six examples of various exposure assessment studies are described. The field examples are chosen to show the broad variety of situations that calls for exposure assessment studies to be performed. The first study describes *exposure assessment of air pollution in Delhi, India*, with the purpose of linking exposure with health effects (respiratory morbidity). The second study is an example of a cross-sectional *total exposure assessment study of lead in children of Mexico City*. The study was performed in order to identify major sources and pathways for lead exposure and to evaluate the contribution of these sources to the total lead exposure. In the third field example of *pesticide exposure assessment in Costa Rica*, epidemiological studies were performed to describe and quantify the pesticide related health problem. The fourth field example describes a method of *retrospective exposure assessment in an industrial setting*. The exposure assessment was carried out in order to investigate the exposure response relationship between exposure and health effects (lung cancer). The fifth example is a description of a *chemical accident - the Bhopal disaster* and how exposure assessment and health effects studies were performed retrospectively. The last example describes a large *national exposure assessment study performed in Germany* with the purpose of providing a database for reference values.

Intentionally blank

Air pollution and respiratory morbidity in Delhi, India.

by Sameer Akbar, This study was conducted as part of the author's field work for his Ph.D. as a BEIT Fellow for Scientific Research at the Centre for Environmental Technology, Imperial College of Science Technology and Medicine, London.

Background and objectives

Delhi is known to record one of the highest concentrations of suspended particulate matter (SPM) amongst the world's megacities. Though concentrations of other air pollutants (SO_2 and NO_2) have also been increasing steadily, only SPM is known to consistently violate the WHO standards (Box 2, p. 5). Recent research in developed countries has associated respirable suspended particulate matter (RSPM) with increases in daily mortality and morbidity in cities with average ambient RSPM concentrations in the range $20 \mu\text{g}/\text{m}^3$ - $60 \mu\text{g}/\text{m}^3$, with no apparent indication of a threshold. Measurements in Delhi have shown that the average monthly RSPM levels range between $50 \mu\text{g}/\text{m}^3$ and $420 \mu\text{g}/\text{m}^3$.

The exact meaning of results from research conducted in developed countries for a developing country city like Delhi is clouded by various factors, including differences in relationships between ambient levels and personal exposure, individual time-activity patterns, the physical environment (land use), overcrowding in houses, poor ventilation, and type of domestic fuel used. However, estimates of environmental health risks in developing countries still rely on extrapolation of dose-response evidence from developed countries.

This example reports on the field work stages of a cross-sectional study that was conducted in the winter of 1994-95 (November - March) in Delhi with the objective of classifying exposure patterns, and assessing associations between respiratory health effects and particulate air pollution. The following sections explain the study design and methodology, highlighting the problems encountered during data collection. The concluding section dwells on some study design issues which have a bearing on exposure assessment for environmental epidemiology in developing countries.

Study design

A sample of 3000 respondents was drawn from middle-class housing colonies in three geographical areas of Delhi which differed in land use pattern - residential, commercial-residential, and industrial-residential. In addition to land use pattern, these areas also differed significantly in long-term (1989 - 1993) average SPM concentrations measured at the National Ambient Air Quality Monitoring Station (NAAQMS) located in the area. The residential area had the lowest long-term mean ambient SPM concentration ($321 \mu\text{g}/\text{m}^3$), followed by the commercial-residential ($346 \mu\text{g}/\text{m}^3$), while the industrial-residential ($437 \mu\text{g}/\text{m}^3$) area reported the highest concentration.

The sample was restricted to respondents who were 25 to 45 years old, and were not employed in occupations which carried a risk of occupational exposure. Although 33 % is the commonly quoted prevalence rate in Delhi for “respiratory ailments”, a conservative estimate of 20 % for office workers and 10 % for housewives was used to calculate the sample sizes for different sub-groups.

It is acknowledged that the urban poor are at higher risk of exposure to air pollutants. However, this study focused on the urban middle class because of potential confounding by additional risk factors (e.g. occupational exposure and biomass based domestic fuels) in the lower socio-economic groups, hence requiring a more refined study design and a larger sample size. By focusing on 25 to 45 year olds, it was expected to capture two groups of respondents who differ in time-activity pattern - housewives and office workers, and at the same time look for cause-effect in a sub-group whose health status is not likely to be compromised by age.

Epidemiological survey

Middle-class housing in Delhi usually consists of either apartment blocks or privately owned houses. As opposed to private housing, apartment blocks usually have the inherent advantage of a planned layout, stratification by socio-economic status, and uniformity in housing structure.

Sampling

A door-to-door questionnaire survey was conducted in selected housing colonies in order to collect the relevant information. All interviewers were provided with a sampling protocol in terms of the number of respondents to be interviewed per day, and a systematic random sampling frame. However, certain practical reasons made it difficult to follow a rigid sampling frame.

Firstly, since a majority of door-to-door surveys in urban middle-class housing are carried out by marketing companies, the interviewers were often met with an initial refusal to participate. On the other hand, air pollution being a “topical” issue, there was sometimes a risk of selection bias because of respondents’ enthusiasm. Interviewers were instructed to retry if the respondent initially refused to participate, but to stick to their sampling frame in areas where the participation rates were good.

Secondly, both male and female respondents were found to have a preference for women interviewers. Two specific reasons could partly explain this phenomenon: (i) for socio-cultural reasons, women respondents, especially housewives from conservative households, do not usually talk to male strangers; (ii) despite carrying identification, because of safety concerns male interviewers were often turned away from behind closed doors.

Finally, accessibility of respondents became difficult as interviewers went up the social ladder. Unfortunately, this was found to be correlated with disparity in social class between interviewer and respondent. It is acknowledged in survey research that interviewers should belong to the same social background as the potential respondents. This theory was successfully tested by sending an interviewer from a compatible social background into such housing colonies, and getting a better participation rate.

Questionnaire

The questionnaire elicited information on background, health effects, economic damage, time-activity patterns and personal habits (p. 136).

The background and personal habits sections of the questionnaire were aimed at capturing key socio-economic and socio-cultural factors, some of which could also qualify as risk factors for respiratory morbidity. Incorrect or conflicting responses (between household members) to personal questions often provided moments of comic relief to interviewers: Husbands would often try to lie in front of wives or mothers in order to hide their habit of smoking/chewing tobacco or pan/beetle leaves! Or family members (interviewed separately) would reveal different figures for family income!

Most of the health effects questions were tailored after the British Medical Research Council questionnaire and were aimed at assessing the winter prevalence of symptoms. Data on two week recall of respiratory symptoms were collected so as to assess temporal associations between respiratory morbidity and ambient (particulate) air pollution. Time-activity data were also collected for different micro-environments, which could later be used in conjunction with RSPM measurements to classify personal exposure.

The economic damage section was aimed at assessing the possible economic implications of variation in particulate concentrations. In addition, a section on willingness to pay (based on a hypothetical scenario) was also included in the questionnaire to estimate the monetary value of respiratory morbidity.

The questionnaire was pre-tested on a random sample of 150 respondents in the summer of 1994, and the responses were used to further refine the questionnaire. Four interviewers were trained and made to conduct mock interviews in the week prior to starting the field work.

Exposure classification

The questionnaire survey was accompanied by RSPM monitoring in a sub-sample of the households, in commonly used travel modes (i.e. buses, cars, and three-wheelers), and in the ambient environment.

The objectives of conducting a limited amount of monitoring were: (a) to assess if RSPM concentrations (indoors and ambient) differed significantly in the three areas; (b) to estimate the significance of RSPM concentrations in different micro-environments as a risk factor for exposure; and (c) to use the measurements as a means of exposure classification of respondents based on their time-activity patterns and their mode of travel.

Ambient

Outdoor or ambient measurements of RSPM were made at NAAQM stations, which are located on top of double storey buildings situated within Delhi Electric Supply Undertaking sub-station complexes. However, siting the monitoring stations in the compound of an electric sub-station did not guarantee uninterrupted power supply.

Outdoor SPM measurements were made gravimetrically using a High Volume Sampler. The samplers were operated at a flow rate of 1.1 to 1.7 m³/min in three 8-hourly sessions to get 24-hourly average values. Three Casella™ AFC 124 pumps with a cyclone head and a Whatman GFA filter (2.5 cm diameter) were used for RSPM sampling. The pumps were operated at a constant flow rate of 1.9 litres/minute and were calibrated and checked with a rotameter before and after each monitoring session.

Indoor

The Casella™ pumps were installed at a height of 6 to 8 feet, as close to the human breathing zone as possible. All the indoor monitoring sessions were for continuous eight hour periods. Care was taken to keep the cyclone head free from any obstruction, and away from any prominent source. Since the time period of the study was over the winter months, houses normally kept their doors and windows closed. The only known indoor source of particles in certain homes was the presence of cigarette smokers. However, the geographical location of houses and the siting of monitors indoors was dependent on the respondents' willingness to participate in the microenvironmental monitoring exercise.

A major deterrent to having a monitor installed inside homes was the safety consideration. In some cases respondents had the monitors installed indoors, but panicked when neighbours suggested the possibility of the monitor being an explosive device!

Travel

For travel measurements the pumps were worn on the waist belt by individuals while travelling, and the cyclone was worn on the lapel or upper part of the chest. Except in the case of cars when the driver wore the sampler, it was worn by a passenger in the bus and three-wheeler. The routes travelled were varied in order to cover the major roads to and from the three study areas.

A rigid monitoring protocol was designed so as to evenly distribute the monitoring schedule over the study period. In all, 41 measurements were made in travel microenvironments, 81 measurements were made in indoor microenvironments - 21 with smokers and 60 without smokers, and 44 measurements were made in the ambient environment.

What can be learnt from this example?

An important lesson learnt from the field work is the uncertainty in estimating exposure based solely on ambient air quality data (as is usually done in population-based air pollution epidemiology studies). The difficulty arises primarily because of two reasons - (a) the mixed land use in and around housing colonies, and (b) variation in individual time-activity patterns and travel modes (e.g. buses, cars, two-wheelers etc.) - both of which are important determinants of personal exposure.

Land use violations (e.g. one room industrial units operating in residential areas) can result in residents of adjacent housing colonies having widely different exposure patterns. The contrast between the residential and industrial-residential area in terms of land use is large. In addition, socio-economic and socio-cultural factors which have a bearing on the nature of questionnaire responses tend to be closely linked to land use pattern, with people lower down the socio-economic/cultural ladder residing in mixed land use areas. These intra-urban differentials in socio-demographic factors present significant study design difficulties in a city like Delhi.

This study was a small first attempt, conducted in the face of limited resources. However, it serves to provide important lessons, and highlights the need for a bigger study in order to classify exposure of population sub-groups in a developing country megacity like Delhi. An intensive microenvironmental monitoring protocol coupled with a well-designed epidemiological study could provide the much needed information on varied exposure patterns among population sub-groups across the socio-economic spectrum.

Assessment of Respiratory Damages in Relation to Particulate Air Pollution
QUESTIONNAIRE

Date: (5-10) **Time:**
Respondent I.D.: (11-15) **Interviewer I.D.:**
Screening Questions

(The screening questions are meant to assess the respondents suitability for participating in the survey. It is important to make sure that the respondent understands that only a certain section of the population is being interviewed. This will ensure that people who are not found suitable for the survey, do not get offended.)

- 1.) Age (25-45) _____ (16-17)
_____ (18)
- 2.) a) Professional Status (Housewife/Manager/Business...etc): _____ (19)
(If housewife list husbands professional status)
b) Nature of Job (Office/Shopfloor/....etc): _____
- 3.) Which area do you Work in? _____ (20)

(For the interviewer to read out to the respondent)

The following two page questionnaire will not take more than 15-20 minutes of your time. Please answer the questions in the order I ask them. I would appreciate if you do not read the questionnaire during the interview, unless requested to do so. You can see it once the interview is over. Your co-operation will be appreciated.

NAME: _____
ADDRESS (H): _____ ADDRESS (O): _____

PHONE (H): _____ PHONE (O): _____

Assessment of Respiratory Damages in Relation to Particulate Air Pollution
QUESTIONNAIRE

Date: (5-10) **Time:**
Respondent I.D.: (11-15) **Interviewer I.D.:**
Screening Questions

(The screening questions are meant to assess the respondents suitability for participating in the survey. It is important to make sure that the respondent understands that only a certain section of the population is being interviewed. This will ensure that people who are not found suitable for the survey, do not get offended.)

- 1.) Age (25-45) _____ (16-17)
_____ (18)
- 2.) a) Professional Status (Housewife/Manager/Business...etc): _____ (19)
(If housewife list husbands professional status)
b) Nature of Job (Office/Shopfloor/....etc): _____
- 3.) Which area do you Work in? _____ (20)

(For the interviewer to read out to the respondent)

The following two page questionnaire will not take more than 15-20 minutes of your time. Please answer the questions in the order I ask them. I would appreciate if you do not read the questionnaire during the interview, unless requested to do so. You can see it once the interview is over. Your co-operation will be appreciated.

NAME: _____
ADDRESS (H): _____ ADDRESS (O): _____

PHONE (H): _____ PHONE (O): _____

A.) BACKGROUND INFORMATION

- 1.) Sex: M/F _____ (21)
- 2.) Educational qualification (Number of Years of Education)? _____ (22-23)
- 3.) How many people live in your house (including children)? _____ (24-25)
- 4.) Excluding kitchen and bathroom, how many rooms are there in your house? _____ (26-27)
- 5.) What cooking fuel is used in your house: (a)LPG (b)Kerosene (c)Other _____ (28)
- 6.) What is your time period of residence in the present area (yrs.)? _____ (29-30)

B.) HEALTH EFFECTS

- 7.) Do you suffer from any respiratory allergies? Yes/No (31)
- 8.) Have you ever been diagnosed with any major chest ailment (e.g. T.B./Chronic Bronchitis/Others:.....)? Yes/No (32)

Cough

- 9.) Do you usually cough first thing in the morning in winter? Yes/No (33)
- 10.) Do you usually cough during the day - or at night - in the winter? Yes/No (34)

Phlegm

- 11.) Do you usually bring up phlegm from your chest first thing in the morning in winter? Yes/No (35)
- 12.) Do you usually bring up phlegm from your chest during the day - or at night - in the winter? Yes/No (36)

Asthma/Wheezing

- 13.) Have you ever had attacks of wheezing or whistling in the chest? Yes/No (37)
- 14.) Have you ever been diagnosed as having asthma? Yes/No (38)

Eye Irritation

- 15.) Do you usually have itching in eyes - when you have been out, during winter? Yes/No (39)

- 16.) In the LAST TWO WEEKS how would you rate the intensity of the following symptoms (O) is for occasional, and (F) for frequent

	None	Mild (O)	Mild (F)	Moderate (O)	Moderate (F)	Severe		
a) Dry Cough							(40)	<input type="text"/>
b) Cough with Phlegm							(41)	<input type="text"/>
c) Asthma/Wheezing							(42)	<input type="text"/>
d) Eye Irritation							(43)	<input type="text"/>
e) Breathlessness							(44)	<input type="text"/>
f) Body Ache							(45)	<input type="text"/>
							(46-47)	<input type="text"/>

- 17.) In the last two weeks did you suffer form any other illness or ailment ? (If Yes, please list:.....) Yes/No (48)

C.) ECONOMIC DAMAGE

- 18. a) During the last two weeks did you take any medication to relieve any of the above mentioned symptoms? (If No, goto 19) Yes/No (49)
- b) How much money did you spend on the medication? _____ (50-52)
- 19. a) During the last two weeks did you consult a doctor regarding any of the above mentioned symptoms? (If No, goto 20) Yes/No (53)
- b) How much money did you spend as consultation fee? _____ (54-56)
- 20.) For how many days during the last two weeks could you not goto/do work because of any of the above mentioned symptoms? _____ (57-58)
- 21.) For how many days during the last two weeks was your activity restricted (though you could work) because of any of the above mentioned symptoms? _____ (59-60)
- 22. a) During the last two weeks did you take any vitamins, eat more fruit, or take anything else to relieve any of the above mentioned symptoms ? (If No, go to 23) Yes/No (61)
- b) How much money did you spend on it? _____ (62-64)

D.) TIME-ACTIVITY PATTERN

23.) What is the average number of hours/day that you spend in the following micro-environments :

A.) INDOORS		B.) OUTDOORS	
a) Kitchen	_____ (65-67)	e) Vehicle	_____ (16-18)
b) Office	_____ (68-70)	f) Ambient	_____ (19-21)
c) Home	_____ (71-73)	g) Other	_____ (22-24)
d) Other	_____ (74-76)		
TOTAL	_____ (77-80)	TOTAL	_____ (25-28)

E.) PERSONAL HABITS

24. a)	Do you smoke (<i>If No, go to 25</i>) ?	Yes/No	(29)	_____
b)	How much (<i>daily average</i>)?		(30-31)	_____
25.)	If you don't smoke, are you (severely) exposed to cigarette smoke at home or at work?	Yes/No	(32)	_____
26.a)	Do you chew tobacco/pan masala (<i>If No, go to 27</i>) ?	Yes/No	(33)	_____
b)	How much (<i>daily average</i>)?		(34-35)	_____
27.)	What kind of water do you normally drink ?		(36)	_____
	a)boiled b)filtered c)boiled and filtered d)treated (Aquaguard, zero B etc.)			
	e)ordinary tap water f)others :			
28.)	Do you have any medical insurance?	Yes/No	(37)	_____
29.)	What is the total monthly income of your family (<i>approx. range</i>) ?		(38-43)	_____
30.)	What is your total monthly income (<i>approx. range</i>)?		(44-49)	_____
31.)	What mode of transport do you use for commuting? (a)Bus (b)Car/Jeep (c)Two-wheeler (d)Three-wheeler (e)Cycle-rickshaw (f)Other:		(50-51)	_____
32.)	Do you wear any anti-pollution mask/cover while commuting?	Yes/No	(52)	_____

F.) WILLINGNESS TO PAY

Recent research has shown that suspended particulate is the most damaging form of air pollution for health. As you may know, the level of particulate air pollution in Delhi frequently exceeds the standards set by the World Health Organisation by two to three times. Newspapers have reported that every third Delhiite is suffering from some respiratory illness. Cleaning the air will require many kinds of actions, such as more frequent checks on vehicle exhaust, installation of air pollution control equipment in factories many of which were not designed to accommodate such equipment, or even a better public transport system.

Suppose there was a citywide plan to reduce particulate air pollution. The implementation of this plan would cost money, and citizens like you would have to pay the cost on a monthly basis to maintain the air quality at safe levels. Consider this somewhat similar to paying for water connection in your house. I am now going to ask you about how much you would be willing to pay to help in improving the quality of air that you breathe. It is important that you think carefully about this and give a realistic answer. Please do not agree to pay if you cannot afford it or if you feel you have other, more important things to spend your money on.

I want you to assume that if the plan were implemented, most households like yours in Delhi would pay a similar amount as your household for improving the air quality. Also, assume that industry and government would do their fair share towards the same goal.

33.a)	Would you support such a plan to reduce particulate air pollution, if you were required to pay a certain amount per month ? (<i>If Yes, go to 33c</i>)	Yes/No	(53)	_____
b)	There are several reasons why one might not want to pay anything to implement the plan to reduce particulate air pollution in Delhi. Could you please explain your reasons: (i)Cannot afford (ii)Satisfied with existing situation (iii) Not concerned about air pollution (iv)Governments responsibility (v)Industries responsibility (vi)Other (specify):		(54)	_____
c)	How much would you be willing to pay per month ?		(55-58)	_____

G.) FURTHER PARTICIPATION

34.)	Would you be willing to let us install an air sampler inside your house/office for a minimum of 8 hrs.?	Yes/No	(59)	_____
------	---------------------------------------------------------------------------------------------------------	--------	------	-------

Thanks for your Co-operation !

A cross-sectional total exposure assessment study of lead in children of Mexico City

This field example is mainly based on investigations published by Isabelle Romieu and co-workers (Romieu et al, 1994; 1995).

Background and objectives

Setting

Mexico is the sixth largest lead-producing country in the world, and 40 % of its production is used locally in different industrial processes that cause lead contamination of the environment. Sources of airborne lead in the Valley of Mexico City include lead smelters, battery manufacturing plants, battery repair shops, paint factories and leaded petrol.

It is estimated that about 1500 tons of lead are deposited annually in Mexico City from combustion of leaded petrol (Contreras, 1990). Recognition of this problem has driven the Mexican government to decrease the use of tetraethyl lead in petrol. At present, two types of petrol are used in Mexico, one that contains 0.13-0.26 g/l and one that contains 0.003 g/l (the "unleaded type"). Vehicles can use the unleaded type only if they are equipped with a catalytic converter and if the model is manufactured in 1985 or later. However, among the 3 million vehicles in Mexico City, 80 % were manufactured before 1980 and some before 1970 (Sanchez, 1990). Therefore, despite the introduction of unleaded petrol, consumption of leaded petrol is still high in Mexico City.

Environmental lead pollution and its potential adverse health effects were observed in Mexico as early as 1682 (Cooper, 1980). Lead contamination is a leading public health problem in Mexico. Several epidemiological studies have

reported blood lead levels and risk factors for the population of Mexico City (for references see Romieu et al, 1995). However, information was scarce about the concentration of lead in the environment and the contribution of various sources to the total lead exposure in the population of Mexico City.

Health effects

Lead exposure can result in a wide range of biological effects depending upon the level and duration of exposure (WHO, 1995). Lead adversely affects several organs and organ systems (blood-forming organs, the peripheral and central nervous system (CNS), the kidneys, and the gastrointestinal tract). The effects range from inhibition of enzymes to death.

For metabolic, behavioural and neurological reasons, children are more vulnerable to the effects of lead than adults. Lead passes over the placenta and there are some epidemiological data indicating effects such as pre-term delivery and reduced foetal growth and maturation. Lead has been shown to be associated with impaired neurobehavioural functioning in children. Both prospective and cross-sectional epidemiological studies have been conducted to assess to what extent environmental lead exposure affects CNS-based psychological functions (NRC, 1993). There is no definitive evidence of a threshold, but below the blood lead concentration (PbB) range of 100-150 $\mu\text{g/l}$, the effects of confounding variables and limits in the precision in analytical and psychometric measurements increase the uncertainty attached to any estimate of effect. However, there is some evidence of an association below this range. Most evidence relates to decrements in intelligence quotient (IQ).

Environmental data and sources of exposure

Lead is a multimedia pollutant and is present in air, food, drinking-water, soil and dust. The main routes of human exposure to lead are inhalation and ingestion. The dermal absorption is usually low. An investigation of available environmental data and possible sources of lead exposure was carried out prior to study start.

In Mexico City, there is continuous monitoring of air pollution, including atmospheric lead. In the northern part of Mexico City, near an industrial park, the traffic and industrial emissions are particularly high. Atmospheric lead used

to greatly exceed the national air quality standard for lead in Mexico (1.5 mg/m^3 as a 3 month average). However, since 1990, particulate lead content has decreased substantially, possibly due to an increased use of unleaded petrol and to the closure of several lead-manufacturing industries. In the southern part of the city, a residential area, the atmospheric lead tended to stay below the air quality standard.

Lead in drinking-water may come from contamination at the source, but it can also result from water treatment or from lead in piping, joints, and containers for storage etc. Lead dissolves into the water, especially if the water is acidic. Leaded pipes are common in Mexico, but the water is alkaline. Water samples collected from randomly selected households, using lead-free containers, showed lead concentrations close to $0.1 \text{ } \mu\text{g/l}$ (below the WHO guideline for drinking-water of 0.01 mg/l ; WHO, 1996a), despite the first flush from the tap being collected, to sample water that was standing overnight (worst case approach).

Lead-based paint and pigments that contain lead chromates are frequently used in Mexico. Lead in paint may be released into the environment (soil, dust, water) by deterioration of surfaces and by contact with acid rain and drainage water. In addition, dissociation of lead chromates by gastric acid may contribute to lead uptake in children who ingest contaminated soil and dust. Lead pigments are also used in children's toys and pencils. Different types of coloured pencils have been analysed for lead. Most coloured pencils have a high lead content with a high variation in lead content depending on the pencil's origin. Values between 1 and 68,000 ppm were reported. This source of lead exposure can contribute to the total exposure of children, who tend to bite pencils and therefore ingest paint chips.

Leaded glaze is commonly used in Mexico to cover ceramics that are used to cook, store, and serve foods and beverages. This traditional pottery is hardened at low temperatures, and therefore the lead remains in the glaze and can be released into foods and beverages, especially acidic ones like tomatoes and fruit juices, because the solubility of lead increases at low pH. Experiments have shown that most of the lead released from the ceramics comes from the glaze. The place of origin of the pottery and time of usage of the pottery has also been shown to be important factors for lead content. Values ranging from 89 to 8000 $\mu\text{g/dl}$ of food and beverages have been reported (Hernandez et al, 1991).

Lead-soldered side-seam cans are still available in Mexico. As with food prepared and kept in traditional pottery, acidic foods processed in cans with lead solder are more likely to be contaminated. The lead content in different types of canned foods has been measured. In 1993, in a random sample of 300 cans with different types of solder, about 30 % had a lead content exceeding 0.30 mg/kg, the recommended guideline (FAO/WHO, 1984b). Among these cans, 61 % were lead-soldered.

Food may also be contaminated before processing. High lead content may for example be found in leafy vegetables due to air fallout of lead. Other potential sources of lead exposure are cigarettes, cosmetics, and traditional medicine. Analyses of lead content in cigarettes sold in Mexico showed that cigarette smoking may contribute to lead exposure. Lead-containing cosmetics used by women may contribute to lead exposure of their children. Traditional medicines such as azarcon (used as a treatment for diarrhoea) have a high lead content and have been related to lead intoxication in Mexican children (Baer and Ackerman, 1988).

Objectives

The objective of the study was to identify major sources and pathways for lead exposure in Mexico and to evaluate the contribution of these sources to the total lead exposure in the population of children residing in Mexico City.

Exposure assessment

A cross-sectional study was conducted to determine the contribution of various environmental media to the blood lead levels in children younger than 5 years of age. A random sample of 250 households in each of two areas of Mexico City was selected, and a total of 200 children participated in the study. One of the study areas was a residential area and the other was located within the industrial part of Mexico City. The major sources of lead exposure were expected to differ between these two areas.

All households selected were visited to obtain a sample size of 100 children in each area. The mothers of the children selected were invited to participate in the study, which included the completion of a questionnaire, environmental sampling of their household, and collection of blood samples from each child. Participants were informed of the study objectives and asked to sign an informed

consent form. After all samples were collected, dietary counselling and advice on minimising lead exposure was provided to all participants. Environmental samples of floor, window, and street dust, paint, soil, water, and glazed ceramics were obtained from the participating households, as well as dirt from the hands of the children. Environmental sampling procedures for soil, dust, paint, and water were carried out in accordance with the technique proposed by the Environmental Sciences and Technology Laboratory, Georgia Technical Research Institute (GTRI, 1992). Training of the field personnel and standardisation of procedures were provided by a senior scientist from the GTRI. All procedures were carried out using vinyl gloves in order to avoid contamination of samples. External quality control was provided by the Centers for Disease Control (CDC), (Atlanta, Georgia, USA).

Results

Blood lead levels in children (N=200) ranged from 10 to 310 $\mu\text{g/l}$ with a mean of 99 $\mu\text{g/l}$ (SD 58 $\mu\text{g/l}$). Blood lead concentrations exceeding 100 $\mu\text{g/l}$ were found in 44 % of children aged 18 months or older. Age was significantly related to children's blood lead levels. Blood lead levels were slightly higher in the industrial study area. However, the major predictors of blood lead levels were the lead content of the glazed ceramics used to prepare food, exposure to airborne lead due to vehicular emission, and the lead content of the dirt from the children's hands.

What can be learnt from this example?

In order to decrease lead exposure by control measures, the significant sources of lead exposure have to be determined. Although important measures had been taken in Mexico to reduce lead exposure of the general population (e.g. the introduction of unleaded petrol), the investigators found that lead exposure is still an important problem in Mexico. The findings pointed out that leaded petrol still played an important role in the population's exposure to lead, but that lead-glazed ceramics also played a major role for the total exposure. Thus, it is necessary to inform the public of the risks of lead-glazed ceramics and to regulate their use.

The strategy of this study: 1/ to gather all available environmental data on lead in all exposure media, 2/ to do complementary environmental monitoring when adequate data were missing, 3/ to collect environmental samples from each household included in the study, and 4/ to measure the total lead exposure by biological monitoring in the study population, was adequate to identify the significant sources of lead exposure in children.

Assessment of pesticide exposure in epidemiological studies in Costa Rica

by Carl-Gustaf Elinder and Catharina Wesseling,
Karolinska Institutet, Stockholm.

Background and objectives

Pesticide poisoning in developing countries is an important public health problem. A report from the WHO indicates that globally three million severe poisonings occur annually. Counting mild poisonings, as many as 25 million poisonings might occur in developing countries (Jeyaratnam, 1990).

In Costa Rica, a developing country with an agricultural export-based economy, the per capita annual consumption of pesticides was 4 kg during the 1980s. This was eight times the 0.5 kg estimated world average per capita consumption and some of the most used substances were, according to the WHO's hazard classification, highly and extremely toxic. From field observations in agricultural areas of the country it was obvious that workers did not use protective equipment and that safety procedures during pesticide use were overall inadequate.

In order to more specifically describe and quantify the pesticide related health problems in Costa Rica, an extensive research programme commenced in the middle of the 1980s. This included descriptive epidemiological studies as well as cohort and cross-sectional studies and also aimed at a more detailed exposure assessment (Wesseling et al, 1993; Wesseling et al, 1996; van Wendel de Joode et al, 1996). Registers with data on exposure or health outcomes are rare in developing countries. However, in Costa Rica it is possible to follow up subjects with verified poisonings or other health effects in the cancer or mortality registries.

Exposure assessment and results

In the first population based study exposure categories were, for practical reasons, very crude: those not working at all (non-labour population), non-agricultural workers, and agricultural workers.

Data from three national registers were used: 1) occupational accidents and disease reports in wage earning workers, 2) hospitalisations and 3) deaths. During 1986, 1800 occupational accidents and diseases caused by pesticides were reported; between 1980 and 1986 a total of 3330 persons were hospitalised and 429 died. Cholinesterase inhibitors caused 21 % of the reported occupational accidents, 63 % of the hospitalisations and 36 % of the deaths. Paraquat caused 21 % of the occupational accidents, 24 % of the hospitalisations and 60 % of the deaths. Overall, 25% of the hospitalisations and 11% of the deaths were due to occupational poisonings.

Age and gender specific incidence rates were calculated for the “exposure categories”. Hospitalisations and deaths were 13 and 11 times more frequent among agricultural workers than among the rest of the population. The annual rate for hospitalised pesticide intoxications in Costa Rican agricultural workers was 115 per 100 000, of which about one tenth were fatal. It was estimated that the yearly incidence of symptomatic occupational pesticide poisonings among agricultural workers was 4.5 %. High risk groups for occupational poisonings included workers aged 15-29, female agricultural workers and workers in banana plantation areas.

Two results of this study were considered to be of particular importance. Firstly, pesticide related injuries among wage earning workers were more than six times higher in the banana plantation areas than in the rest of the country. Secondly, contrary to prevailing opinions, paraquat was identified as one of the most problematic pesticides with regards to occupational poisonings. It was also noted that many paraquat injuries occurred on banana plantations. Several studies have dealt with these two issues in recent years by assessing both exposure and health effects.

Next, exposure among banana workers were assessed. Banana production is a major component of the export industry in Costa Rica. Pesticide use has been

substantial on banana plantations for decades and many work tasks include different types of exposures. Efforts were made to characterise pesticide exposures of plantation workers through the analysis of import and pesticide use data as well as observations at the work place. Detailed data were collected regarding types of pesticides, frequency of use, amounts applied and use practices in relation to job-titles (Chaverri and Blanco, 1995; Vaquerano, 1995; van Wendel de Joode et al, 1996). After that, accurate numbers of workers per job-title, per area and per time unit were determined in order to produce reliable population data for the calculation of job specific incidence rates (Wesseling et al, 2001). Herbicide and nematocide applicators, cleaners of the water basins at the packing plants, flaggers guiding the crop dusting airplanes and storehouse workers were the five job-titles with the highest risks for pesticide related illness. Several quantitative exposure studies were also carried out on banana plantations. One study quantified exposure and dose in 11 paraquat sprayers and identified determinants of exposure by means of measurements, observations and interviews (van Wendel de Joode et al, 1996). Skin exposure was measured by skin pads, respiratory exposure by personal air sampling and absorbed dose by urine sampling. It was found that protective clothing did not effectively protect against dermal exposure. Both dermal and respiratory exposure were significantly related to dose and both should be considered possible routes for systemic absorption of paraquat. During the field work hazardous situations which in theory could result in severe systemic poisonings were observed frequently. Seven of the eleven spray operators had experienced one or more health complaints during the last twelve months that they associated with paraquat (skin burns, eye irritations, nail damage, nose bleeds, burning sensation in nose cavity and non-specific systemic symptoms). The occurrence of adverse health effects could not be excluded at the measured levels of exposure and, considering also the frequent high risk situations, it was concluded that paraquat is not safe for occupational use.

Another study assessed the exposure of packing plant workers who also had been identified as a high risk group. Skin and eye lesions occur frequently among the mostly female workers who select and wash the bananas at the water basins of the packing plant and some of whom spray fungicides on the bananas with a hose before they are placed in the boxes. Residues of the fungicides thiabendazole and imazalil were measured in skin pads (averages of 4.7 and 6.0 mg/day, respectively, of total dermal exposure) and in the water of the basins at the packing plant (Vaquerano, 1995). It is likely that the observed high incidence of topical

lesions (allergic and irritant contact dermatitis and severe chemical burns) in these workers is associated with skin contact with the spray mist, as well as with the contaminated water of the basins (Wesseling et al, 2001).

More specific health effects from pesticides in banana workers have been examined in cross-sectional, cohort and case studies. The exposure circumstances of a series of fatal non-intentional paraquat poisonings were analysed in the context of developing country labour conditions, with emphasis on the potential danger of dermal absorption and the amount of paraquat needed to produce a fatal outcome in case of oral intake. The medical records and autopsy protocols of 15 fatal non-intentional poisoning cases among agricultural workers were reviewed and relatives were interviewed. The results of this study suggest that paraquat may cause fatal poisonings by ingestion of small amounts, by dermal absorption of diluted paraquat, and possibly by inhalation (Wesseling et al, 1997).

The cancer risk among banana workers was examined in a cohort study of employment status during the time DBCP, a particularly toxic pesticide, was used. Employment status was based on the payroll reported to Social Security between 1972-1979. Exposure indicators were duration of employment (number of months), and first year of employment. The results, revealed an increased mortality in certain types of cancers in the exposed group as compared to the general population of Costa Rica (Wesseling et al, 1996). No exposures to specific pesticides could be identified. Currently a cohort study of workers with confirmed DBCP exposure and low sperm-counts is being carried out.

In addition, neurotoxic effects among workers previously poisoned with cholinesterase-inhibiting pesticides have been examined in a cross-sectional study based on patients who have been given medical treatment. Exposure category was based on the type of cholinesterase inhibitor (organophosphates versus carbamates). A cumulative exposure index that assesses life time pesticide exposure and which was based on interview data from the study subjects was established. The interview data provided information about duration and frequency of exposures (number of years and number of days per year) for different job-titles. Observations and historical data provided information about the types of pesticides and fraction of the day exposed per job-title. Observations and measurements of exposure under current labour conditions have now to be considered as baselines for retrospective quantitative exposure estimates by judgement of differences by an occupational

hygienist (Wesseling, 1997). Severity of the poisoning was used as a measure of degree of exposure: we tried to use symptoms and signs recorded by physicians in the medical records, categories of hospitalised versus non-hospitalised, number of doses of atropine, days of sick-leave: all these data turned out to be too deficient to be usable as exposure indicators. Finally the number and types of cholinergic symptoms (during the poisoning episode) referred by the worker at the time of testing (checklist with yes-no answers) were used as a measure of intensity of exposure, but the information source is more subjective and therefore maybe less reliable (Wesseling, 1997).

What can be learnt from this example?

Costa Rica is privileged with health registers as compared to other developing countries, which makes it attractive to carry out epidemiological research not possible elsewhere in the developing world. However, opportunities to find sources of information on exposures are present everywhere and health effects can be assessed in many other ways besides by the use of disease registries. These opportunities should be looked for in a creative way. However, it is not sufficient to merely look at the health effects - one also has to assess exposure in one way or the other, the more detailed the better. The examples from Costa Rica given here illustrate this, and also that this type of research frequently produces results that make it evident that specific actions are needed to decrease exposure and risks (Rodríguez et al, 1995).

Intentionally blank

Industrial setting - The Rönnskär case

This case study is mainly based on investigations published by Lars Järup and co-workers (Järup et al, 1989; Järup and Pershagen 1991).

Background and objectives

Setting

The Rönnskär copper smelter in the north of Sweden has for a long time been known as “the dirtiest industry in Sweden”. It was established in 1928 to process ore from the Boliden mine. The ore was highly complex and was rich in arsenic (up to 20 %). The mining company bought two small islands just outside the coast from the local community. The idea was that the winds would carry the emissions from the smelter out to sea, thus minimising the environmental air pollution and the fallout on the surrounding soil.

Exposure

The work environment was heavily polluted with many compounds; it was said that the workers were exposed to “half the periodic system”. The main pollutants connected with health problems at the factory were arsenic, sulphur dioxide (sulphuric acid) and lead. Nickel, bismuth and selenium, as well as other contaminants, were also present in some instances. The main concern regarding environmental exposure has been related to arsenic and sulphur dioxide.

Occupational health effects

Since the start of the smelter operation, both acute and chronic health problems have been registered. Early health effects at the smelter were etching injuries, perforation of the nasal septum and chemical bronchitis. Acute effects, in a few

cases leading to death, after heavy exposure to arsenic have been recorded since the 1930s, the latest casualty occurring as late as in 1985, when a worker was accidentally buried in a pile of arsenic trioxide. He died within 12 hours of the acute exposure.

The main chronic health effects were nerve lesions, reproductive defects and lung diseases. The most important health outcome was lung cancer, and increased lung cancer risks were reported in several studies from the smelter.

Environmental health effects

Lung cancer was the main health effect due to smelter emissions in the surrounding environment. An increased risk of lung cancer was found in non-occupationally exposed individuals in the local communities around the smelter.

Objectives

The main objective of the epidemiological study described in this field example was to investigate the exposure-response relationship between occupational exposure to arsenic and sulphur dioxide and lung cancer risk. The field example describes the method for retrospective exposure assessment, essential for the success of the epidemiological analyses. The field example also briefly describes the environmental exposure assessment for the studies of environmental exposure to arsenic and lung cancer risk that were carried out in the Rönnskär region.

Exposure assessment - occupational

Arsenic and sulphur dioxide

The exposure assessment covered arsenic, sulphur dioxide and to a lesser extent some other compounds (e.g. asbestos, chromium, lead, nickel and tellurium), occurring more or less frequently at various workplaces within the smelter. A report prepared by the chief hygienist at the smelter described the work environment and how the conditions have changed since the smelter started its operation in 1930.

Quantitative data were estimated mainly for arsenic and sulphur dioxide. The assessment was made from historical documents, such as work safety committee reports and internal company papers concerning the work environment at the smelter. Interviews with older workers and managers were also made. The first air measurements were made in 1945. Regular monitoring of the workroom air was carried out from the middle of the 1950s. The early air measurements revealed very high arsenic concentrations at certain work sites, such as the roaster, where an average of 0.9 mg/m³ was recorded (range 0.04-7.1). A few measurements at the gas purifier revealed an average arsenic concentration of 25 mg/m³. Before the commencement of air measurements, statistics from sick leave due to etching injuries, in conjunction with the other historical data mentioned above, were used to quantify the amounts of arsenic in the workroom air.

The arsenic content in the Boliden ore was extremely high (up to 20 %) at the beginning of the operation. The working conditions in the early days were also very poor as evidenced by the sick leave figures mentioned above. It was not until after the second world war that radical improvements were made. The arsenic contents in workroom air were then gradually decreased as the regulatory demands became more rigorous. Exposure data were estimated for three time periods, the first period being 1928-1939, the second 1940-1949 and the third 1950 and onwards, with some variations depending on work-site.

Respirator usage was very limited and virtually non-existent before the second world war. When respirators were used, a piece of cloth often had to suffice. No adjustment of the exposure data was therefore made for the use of respirators.

Smoking

For the collection of information on smoking habits, a postal questionnaire was sent to the next of kin to the cases and referents in a nested case-control study performed within the Rönnskär cohort (described earlier). Information of smoking status was obtained for all study subjects. To assess the total amount of inhaled tobacco for each smoker, pipe tobacco and cigars were "converted" to cigarettes. One cigar was thus considered equivalent to 4 cigarettes, and one package a week of pipe tobacco was regarded to be equal to 7 cigarettes/day.

Exposure assessment - environmental

Measurements of metal concentrations in suspended dust were made at several outdoor measuring stations, up to 7 km from the smelter, since the late 1960s. The ambient air levels of arsenic and lead were mostly below $0.5 \mu\text{g}/\text{m}^3$ as a monthly average, but a few values exceeded $1 \mu\text{g}/\text{m}^3$. No measurement data were available for the time periods when the smelter emissions were at their highest. Analyses of metals in soil and plants show that dust fallout primarily takes place within 10-20 km from the smelter. With this information and the prevailing wind directions (north-south), two parishes near the smelter were chosen as the exposed area in the environmental epidemiological study. The remaining part of the county to which these parishes belong constituted the reference area. Both the exposed and reference areas were sparsely populated with scattered villages, but they also contained some urban districts.

Results

The retrospective exposure data for the different time periods were used together with detailed information of the work history to compute cumulative exposures to arsenic and sulphur dioxide for each worker in the cohort. Standardised mortality ratios (SMRs) were then calculated for several exposure categories using age-specific mortality rates from the county where the smelter was situated. A positive dose-response relationship was found between cumulative arsenic exposure and lung cancer mortality with an overall SMR of 372 (304-450, 95% confidence interval).

Smoking standardised relative risks ranged from 0.7 to 8.7 in different exposure groups. A negative confounding by smoking was suggested in the higher exposure categories. The interaction between arsenic and smoking for the risk of developing lung cancer was intermediate between additive and multiplicative, and appeared less pronounced among heavy smokers.

There was no evident dose-response relationship between estimated exposure to sulphur dioxide and lung cancer.

An increased lung cancer risk (RR= 2.0) was also seen among men who had lived within approximately 20 km from the smelter. The increased risk could not be explained by smoking habits or occupational background.

What can be learnt from this example?

In order to reveal exposure-response patterns in epidemiological studies, a thorough and detailed exposure assessment is essential. The procedure described in this example is, however, very time-consuming and needs the active participation of an experienced (industrial) hygienist. In this example, the investigators had access to detailed data on exposures as well as job histories. This may not always be the case and thus, before an attempt is made to embark on a study of retrospective exposure assessment, the available data should be thoroughly examined.

If, however, the necessary data are available, the effort to create a detailed exposure matrix may be worth while. The clear exposure-response pattern that was revealed in the occupational epidemiological study made it possible to refine the risk assessment for lung cancer caused by occupational arsenic exposure.

Intentionally blank

A major chemical accident - The Bhopal Disaster

This case study is mainly based on an investigation published by P. Cullinan and co-workers (Cullinan et al, 1997)

Background

During the night between the 2nd and 3rd of December, 1984, there was a leak of a poisonous gas from a tank at the Union Carbide's plant in Bhopal in India. The accident proved to become the worst accident so far of this kind in history, killing over 3800 people.

It was a nightmare situation; hundreds of thousands of people living in the close vicinity of a big chemical industry, where safety precautions were poor, and no plans had been made in advance for the event of poisonous gas emissions. The carbamate insecticide carbaryl, or Sevin as the Union Carbide Corporation trade name is, was produced in the plant. Methyl-isocyanate (MIC), a well known toxic substance, was an intermediate in the production.

MIC is a low molecular organic isocyanate (MW 57.05). It is volatile (boiling point $+39^{\circ}\text{C}$) and colourless, with an unpleasant odour. The vapour density is 2, i.e. twice as heavy as air, and it reacts violently with, for example, water in an exothermic reaction. It is a strong irritant. The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) is 0.02 ppm.

The cause of the gas leak was a chemical reaction leading to increased pressure in a tank that contained approximately 27 tonnes of stored MIC, and the opening of a safety valve on the tank. The safety valve remained open for nearly two hours, and tons of MIC in vapour and liquid form was discharged. The meteor-

logical conditions were very unfavourable, aggravating the consequences of the release; air temperature of around + 10° C, light wind from north to north west of 1-2 m/s and a temperature inversion. Not only people in the shanty town close to the plant, but also a great deal of the total population of Bhopal were hit by the gas. The gas rolled slowly across the road into the shanty towns opposite the plant. The sleeping residents were not warned of the leak and the houses and huts did not give any protection. The gas cloud spread further towards the railway station, the police station and downtown. At the railway station, 1.5 km from the plant, more than 100 persons were found dead. The area with the largest number of dead and severely injured was 6-7 square kilometres south to south west of the plant. Severe but not deadly injuries were found in a region of about 25 square kilometres in size. Many of the people exposed to the gas died in their sleep or when they tried to run away from the gas cloud, thus increasing the exposure of their lungs to the gas by taking deep breaths.

Health effects

The acute clinical picture was transient irritation and redness of the skin, intense irritation from the eyes, including bleeding, profuse eye lid oedema and superficial corneal ulceration. Respiratory effects included rhinitis, pharyngitis, coughing, respiratory distress, such as broncho-constriction, shortness of breath and choking. Many patients died from choking or circulatory collapse. Pulmonary oedema developed in many patients in the acute stage. In others pulmonary oedema developed later, after a free interval, but all the patients developing pulmonary oedema presented initial symptoms from the respiratory tract. All types of complications from the respiratory tract were observed, such as pneumothorax, subcutaneous and mediastinal emphysema, bronchopleural fistulas, secondary infections etc. Malaise and vomiting were common signs in the initial stage, probably due to swallowed dimethyl-urea, a product from MIC and water, which was formed when MIC reacted with the water of the mucous membranes of the mouth and oropharynx. It has also been discussed if the gas affects the central nervous system (CNS), circulation, liver and other organs.

The treatment given to affected eyes was irrigation, homatropine to prevent secondary complications, antibiotics and in some cases corticosteroids. Respiratory distress symptoms and pulmonary oedema were treated according to symptoms with oxygen, bronchodilators, diuretics and corticosteroids. When steroid treatment was stopped after 2-3 days, pulmonary oedema returned in approxi-

mately 40 % of the patients. The steroid therapy was started again and pulmonary oedema resolved.

The rescue operation

The organisation of the rescue operation was started as soon as the severity of the accident became apparent. In the beginning everything was chaotic, with thousands of patients streaming into the hospitals. A few hours after the accident the Minister of Health and the Mayor of Bhopal were gathered along with the superintendent and other doctors of leading positions at the Hamidia Hospital. Approximately 300 doctors and 800 medical students also arrived there. Medical teams treated patients in the hospital gardens as it was impossible to get all the patients inside the hospital.

During the first 24 hours, the Hamidia Hospital took care of about 15 000 patients and the J.P. Hospital 25 000 patients. In total around 100 000 patients were given some kind of medical treatment during the first 24 hours. It is difficult to get exact figures but the approximate numbers of dead and injured may be as follows:

- 500 persons died before getting any medical treatment at all
- 6000 persons were severely injured, presenting symptoms such as advanced respiratory distress combined with signs from the CNS and circulatory system. Of these 2000 died within the first week. Total mortality was 3828
- 100 000 persons presented severe symptoms from the eyes and the respiratory tract but were otherwise unaffected
- 19 000 persons are considered to suffer from permanent injuries

Obviously, the catastrophe also had severe psychological and social effects.

Exposure and health assessment

Recently, and ten years after the catastrophe, a follow up was made of a random sample of adults still living in the vicinity of the plant (Cullinan et al, 1997). This revealed that severe lung effects persisted in a large proportion of those individuals who were exposed in 1984, but survived.

In the cross-sectional study, which was carried out during a remarkably short time period, 9 days, 454 adults were examined. Subjects living at different distances from the gas leak during the disastrous night were identified using four concentric zones of 2, 4, 6, and 8 km radius, centred on the Union Carbide factory. An area outside the city with similar socio-economic composition was also identified and served as a control. From each of these areas a random sample of houses was selected. In each selected house, one of the adults (18-60 years of age) present who had been a resident in Bhopal in 1984 was asked to complete a questionnaire, which was administered by trained Hindi speaking interviewers. Subjects were asked about details of the exposure to the gas, current and past health, in particular symptoms from the respiratory system, smoking, and socio-economic factors. All the selected persons agreed to participate. Place of residency at the time of the gas leak was confirmed from official records. Twenty percent of those interviewed were also invited to undergo spirometry using a rolling seal spirometer. An experienced doctor instructed the subjects and made it possible to produce at least two acceptable recordings.

Results

The results were striking. Complains of dyspnoea (difficulty in breathing) and coughs were very common, 95 % and 71 % respectively among those living in the zone close to the plant (0-2 km), and this dropped stepwise to 49 % and 17 % in the control area (>10 km). Likewise forced expiratory flow between 25 % and 75 % of vital capacity (FEF_{25-75}), and other objective measures of respiratory function, were lower in individuals living close to the plant, and increased (improved) with increasing distance (Figure 27).

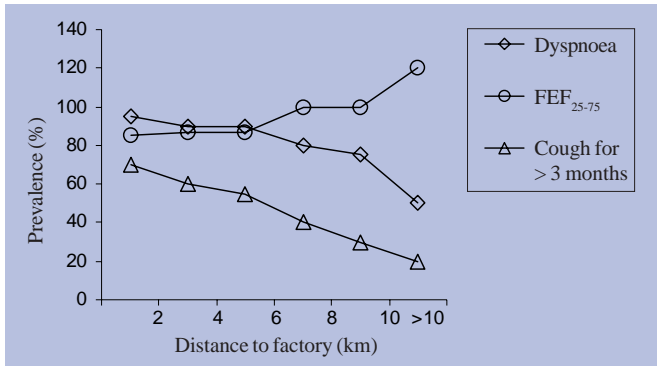


Figure 27. Prevalence of dyspnoea, cough, and forced expiratory flow (FEF) in relation to distance to the factory (data from Cullinan et al, 1997).

What can be learnt from this example?

The important study by Cullinan et al (1997) shows that, if carried out appropriately, very important information with significant implications for health promotion, planning and care can be obtained with limited resources in time and funding.

The tragedy in Bhopal has shown how dangerous an irritant gas can be and what symptoms there will be after a release of this magnitude, when a huge population is exposed. The population living in the vicinity of potential chemical hazards must be given information about any hazardous substances, their properties, alarm signals, how to protect oneself in case of an accident etc. It is striking, and very tragic, that much of the mortality and morbidity could have been prevented by the simple covering of the face with a wet cloth, as MIC decomposes in contact with water. People must be instructed to walk and not to run out of a gas cloud, to walk perpendicular to the wind and to hold a wet handkerchief or a wet rag over the mouth and nose. In some cases it is better to stay inside buildings with closed windows and ventilation turned off.

A chemical accident can be associated with special problems:

- Rescue operations in the risk area are impossible without special protective clothing
- Symptoms from the eyes and lungs make escaping more difficult
- The patients must be decontaminated as soon as possible and always before they can be brought into hospitals
- Roads and also hospitals may be situated in the risk area and may in this way be useless

The normal resources may be quite insufficient and it can be necessary to open up temporary satellite hospitals. On the other hand, the injuries from the toxic gas will often be of the same kind for all victims, but at different stages and of different magnitudes. The treatment can therefore in many ways be standardised.

Information about the accident must be given very soon and continuously on the radio, in loud speakers etc. It must include answers to questions like what is going on, what to do, how long will it last, where to get help, when will help arrive, how to protect oneself etc.

Organisations taking part in life saving actions, like fire brigade, police, medical teams and civilian defence, do not always have knowledge of first aid in case of chemical accidents. Thus, regular training on chemical accidents must be given at all levels of the rescue team so that they are familiar with the situation in the case of an accident.

From the disaster we should learn that when toxic substances are produced, handled, or as was the case in Bhopal as well as in Seveso, produced as a by-product or contaminant during the process, it is very important to be prepared for a possible accident.

The German Environmental Survey (GerES)

by Bernd Seifert, Kerstin Becker, Christian Krause, and Christine Schulz. This case study is based on investigations carried out at the Institute for Water, Soil and Air Hygiene, Berlin.

Background and objectives

Frequently, knowledge about exposure levels of the population is obtained by extrapolation from either work place situations or studies of selected population groups living under specific environmental situations. To obtain a more reliable and representative picture for Germany, the German Environmental Surveys (GerES) were carried out by the Institute for Water, Soil and Air Hygiene of the Federal Environmental Agency with support from the Federal Ministry for the Environment, Nature Conservation and Reactor Safety.

The German Environmental Survey was conducted for the first time in 1985/86 taking advantage of the availability of a representative population sample of the German National Health Survey. A second campaign was performed in the former German Federal Republic (GFR) in 1990/91 which was complemented by a similar programme in the former German Democratic Republic (GDR) in 1991/92. One of the main objectives of the GerES was to determine the exposure to pollutants (predominantly heavy metals), and the resulting body burden of adults and children with the aim of providing a database for reference values.

Study design

The basis for sampling was the German population as registered at the local registration offices. A cross-sectional sample was selected using a two-step random procedure. In the first step all communities were classified into seven categories according to size. In 1985, 100 sample points were selected in 55 communities while in 1990/92, 150 sample points were chosen in 121 communities. In the second step, the subjects were chosen representatively with regard to age and gender in each sample point.

To avoid seasonal effects the sampling was done over a period of one year. The route-plans of the field teams were laid out in such way that confounding by regional effects was excluded.

The final set included 2731 GFR adults (between 25 and 79 years) in 1985/86 and 4287 adults from both GFR and GDR (same age range) in 1990/92. In addition 736 children between the ages of 6 and 14 years who lived in the households of the adults took part in the study. Fully completed questionnaires were available for 73 % of the study participants in 1985/86 and for 63.1 % (GFR) and 69 % (GDR) of the 1990/92 participants.

Exposure assessment

The study included several of the methodological tools that are currently being used in human exposure assessment: questionnaires, human biomonitoring, and sampling and determination of pollutants in the participants' environment. Emphasis was put on the home environment but the water supplied by the local waterworks and the dust deposits outdoors were also analysed. Furthermore, measurements of volatile organic compounds (VOC) and formaldehyde in indoor air, personal sampling of VOC and determination of the dietary intake of various pollutants were carried out.

Questionnaires

Different questionnaires had to be filled in either by the subjects themselves or with the help of trained interviewers. The questionnaires consisted of about two hundred questions about social factors, smoking habits, potential sources of exposure in the domestic and general environment and nutritional behaviour.

Biological monitoring

The concentration of various pollutants and trace elements were analysed in blood (lead, cadmium, copper, mercury), morning urine (arsenic, cadmium, chromium, copper, mercury, nicotine and cotinine), and scalp hair (aluminium, barium, lead, cadmium, calcium, chromium, copper, magnesium, phosphorous, strontium, zinc, nicotine, cotinine).

Domestic environmental monitoring

In both surveys a number of parameters characterising the subjects' domestic environment was studied: the dust deposit indoors, the concentration of trace elements in vacuum cleaner bags and in household tap-water (standing and flush water samples).

In 1985/86 the concentration of VOC in the air of 479 participants' homes was determined by passive sampling (subjects of 5 randomly selected households of each sampling point were asked to participate). In a study of indoor exposure to formaldehyde, 329 randomly selected subjects took part.

Personal air sampling and diaries

In 1991 a sub-sample of 113 persons took part in a study to assess exposure to VOC by personal sampling. For one week the subjects wore passive samplers and simultaneously documented the length of time spent indoors, the room characteristics and any specific exposure such as that caused by renovation activities.

Dietary intake

In 1991 a sub-sample of 318 persons took part in a 24 hour duplicate diet study to examine the dietary intake of a number of elements (Al, As, Cd, Hg, Ca, Cr, Cu, Fe, K, Mg, Mn, Na, Ni, Pb, Zn), and of nitrate and nitrite.

Chemical analysis and quality assurance

Training of the field personnel and standardisation of field procedures were provided by senior scientists of the Institute for Water, Soil and Air Hygiene. All materials used for sample collection, sample preparation and analysis were proved not to be a source of the substances to be analysed. Analyses were carried out by atomic absorption spectrometry (AAS), inductively coupled plasma atomic emission spectrometry or mass spectrometry (ICP-AES or ICP-MS) and gas chromatography (GC). For internal quality control, different standard reference materials were run together with the samples on a daily basis. For blood and urine, external quality control took place by regular participation in round robin tests (interlaboratory comparisons of analytical results) organised by the German Society for Occupational and Environmental Medicine.

Data treatment

The statistical data analysis was performed using descriptive methods as well as methods of statistical inference. Characteristics of the frequency distributions (percentiles), geometric means and confidence intervals of the concentrations of the elements and pollutants in the different media were calculated for the entire sample as well as for sub-samples stratified by gender, age, personal behaviour and by other exposure related factors. Statistical tests were carried out to test for significant differences of the geometric means of the sub-samples. Following the IUPAC recommendations for scientific representation of reference values, 95 % confidence intervals for the 0.95 fractiles were calculated for all elements.

For certain elements (arsenic, cadmium, lead, mercury) in blood, urine and house dust, multiple regression analysis was carried out to identify relevant sources of exposure.

Data were logarithmically transformed to approximate a normal distribution suitable for statistical inference. Concentrations lower than the quantification limit were set to half of the quantification limit. To match the study population with the general population, e.g. in terms of gender and age distribution, a weighting procedure was applied. The adjustment refers to the 1991 Micro Census in Germany.

Results

Comparison of the data of the GerES in GFR of 1985/86 and 1990/91 permits detection of temporal changes in the body burden of the population on a representative basis. Due to the implementation of measures to reduce hazardous pollutants, the mean lead and cadmium levels in blood and hair had decreased between 1985/86 and 1990/91. Similarly the mean concentrations of arsenic in urine, pentachlorophenol (PCP) and lindane in house dust, and lead and cadmium in tap water went down.

The comparison of the results of the surveys in 1990/91 in GFR and 1991/92 in GDR allows regional differences to be detected. A comparison of trace elements in blood and urine of the adults in both parts of Germany showed that in GDR the mercury concentration in blood and urine, as well as the cadmium, chromium and copper levels in urine, were significantly higher ($p < 0.001$) than in GFR. The blood lead level was identical in both samples (geometric mean 45 $\mu\text{g/l}$).

A comparison of the body burden of children showed somewhat different results. In GDR the mercury concentration in blood and urine and the cadmium concentration in urine were significantly higher ($p < 0.001$) than in GFR. In GFR the blood lead level as well as the arsenic concentration in urine were slightly higher ($p < 0.05$) than in GDR.

In 1990/92 the geometric means of the metal concentrations in the blood of the German adult population amounted to 45 $\mu\text{g/l}$ for lead, 0.36 $\mu\text{g/l}$ for cadmium, 0.95 mg/l for copper, and 0.51 $\mu\text{g/l}$ for mercury. These levels are similar to the results of other European studies. For children the metal concentrations in blood amounted to 32 $\mu\text{g/l}$ for lead, 0.14 $\mu\text{g/l}$ for cadmium, 0.98 $\mu\text{g/l}$ for copper, and 0.33 $\mu\text{g/l}$ for mercury.

The concentrations in urine of the adult population (expressed in $\mu\text{g/g}$ creatinine) were 4.6 for arsenic, 0.21 for cadmium, 0.12 for chromium, 6.9 for copper, 0.4 for mercury and for children 4.3 for arsenic, 0.06 for cadmium, 0.14 for chromium, 9.5 for copper, and 0.4 for mercury.

The results of the determination of nicotine and cotinine in urine and scalp hair showed that these substances are useful biomarkers to determine different levels of active and passive smoking. In general the levels of nicotine and cotinine in urine were higher in GFR than in GDR.

The concentration of PCP in house dust was higher in GFR whereas the lindane concentration in house dust was higher in GDR (PCP: 0.37 mg/kg vs. 0.16 mg/kg; lindane: 0.82 mg/kg vs. 0.15 mg/kg). These results can be explained by different usage patterns of products containing these substances.

Elevated lead concentrations in tap water were found in some homes, the limit value of 40 µg/l having been exceeded in 2.2 % of all samples (after overnight stagnation). One of the reasons for the limit-exceeding values may be found in the presence of lead pipe systems for drinking-water distribution which are still used in about 5 % of the households of the German population (10 % in GDR and 3.4 % in GFR).

The daily intake of arsenic, lead, cadmium and mercury corresponds to a large extent to the data determined by duplicate studies in other European countries. The provisional tolerable weekly intake (PTWI) as defined by the FAO/WHO was used to compare the daily dietary intake with guideline values. The mean intake of lead was 32 µg/day and corresponds to 12 % of the PTWI. For cadmium and mercury the mean intake corresponds to 9.4 % (7 µg/day) and 13 % (7 µg/day), respectively.

The results of personal sampling showed that of the various types of environment the workplace has the highest impact on exposure to VOC. Other important factors that need to be considered are renovation activities, use of paints and lacquers as well as frequent reading of newspapers and journals. Smoking contributes significantly to human exposure. In the case of benzene, the multivariate model contained five variables: two related to smoking and three related to vehicle traffic/residential area. The two smoking variables alone explained 20 % out of a total variance of 40 % that could be explained.

What can be learnt from this example?

The results of the GerES have provided, inter alia, a most useful set of reference data to characterise population exposure which are extremely valuable in the evaluation of the results of smaller studies addressing specific problems. The data of the GerES were used for a number of risk assessments, for example in the case of copper in drinking-water and liver cirrhosis in early childhood, and the presence of mercury in amalgam fillings.

The GerES allow the success of abatement measures to be quantified, as could be shown in a number of cases: The reduction of lead concentration in petrol and of industrial cadmium emissions resulted in a decrease in lead and cadmium, respectively, in the blood of the general population and the ban on PCP led to a decrease in PCP in house dust.

Intentionally blank

Continuing your education in human exposure assessment

Human exposure assessment is a growing scientific field, which interrelates with many scientific specialities, as discussed in this book. The scope of this textbook is to give an introduction to the field and how it relates to other specialities. More information is available in textbooks and journals, from organisations such as the WHO, the International Society of Exposure Analysis (ISEA), the International Society of Environmental Epidemiology (ISEE), and via Internet. Criteria documents, such as the WHO IPCS (International Programme on Chemical Safety) Environmental Health Criteria (EHC) documents, summarise available information about environmental levels of hazardous agents and human exposure data. An EHC on Human Exposure Assessment has recently been prepared (EHC 214). A list of EHCs is available via the WHO web site (<http://www.who.int>).

Other organisations and agencies that provides information useful in human exposure assessments are the International Agency for Research on Cancer (IARC), the Agency for toxic Substances and Disease Registry (ATSDR), and the United States Environmental Protection Agency (US EPA). Below are listed some references to relevant books and journals useful for people with a special interest in human exposure assessment.

Environmental Health Criteria 214: Human Exposure Assessment (2000). International Programme on Chemical Safety, World Health Organization, Geneva. 375 pp.

Environmental Epidemiology: A Textbook on Study Methods and Public Health Applications (1999). Baker D, Kjellström T, Calderon R, Pastides H, eds. Preliminary Edition. WHO/SDE/OEH/99.7. World Health Organization, Sustainable Development and Healthy Environments, and United States Environmental Protection Agency. World Health Organization, Geneva. 342 pp.

Exposure Factors Handbook (1997). United States Environmental Protection Agency, Washington DC, USA. (EPA/600/P-95/002Fa). The handbook is available via Internet, US EPAs web site (<http://www.epa.gov>).

Assessment of exposure to indoor air pollutants (1997). Jantunen M, Jaakkola JJK, Kryzanowski M (eds.). WHO regional Publications, European Series, no. 78. WHO Regional office for Europe, Copenhagen.

Linkage Methods for Environment and Health Analysis. Technical Guidelines (1997). Edited by Corvalán C, Nurminen M and Pastides H. WHO/EHG/97.11. World Health Organization, Geneva. 153 pp.

Linkage Methods for Environment and Health Analysis. General Guidelines. A Report of the Health and Environment Analysis for Decision-making (HEADLAMP) Project (1996). Edited by Briggs D, Corvalán C and Nurminen M. WHO/EHG/95.26. World Health Organization, Geneva. 136 pp.

Ethical and Philosophical Issues in Environmental Epidemiology (1996). Special issue of Science of the Total Environment, vol. 184, no. 1-2.

Basic Epidemiology (1993). Beaglehole R, Bonita R, Kjellström T. World Health Organization, Geneva. 175 pp.

Guidelines for Exposure Assessment (1992). United States Environmental Protection Agency, Washington, DC, USA (EPA/600Z-92/001). The guidelines are available via Internet, US EPAs web site (<http://www.epa.gov>).

Principles of Exposure Measurement in Epidemiology (1992). Armstrong BK, White E and Saracci R. Oxford University Press, Oxford, England.

Making Use of Environmental Exposure Databases (1992). Special issue of Archives of Environmental Health 47 (6).

Methods for Assessing Exposure of Human and Non-human Biota. Scope 46 (1991). Tardiff RG, Goldstein BD (eds.). IPCS Joint Symposia 13, SGOMSEC 5. John Wiley & Sons, Chichester, England. 417 pp.

Human Exposure Assessment for Airborne Pollutants. Advances and Opportunities (1991). The National Academy of Sciences, USA. National Academy Press, Washington, D.C., USA. 321 pp.

Exposure Assessment for Epidemiology and Hazard Control (1991). Rappaport SM and Smith TJ (eds). Lewis Publishers, Inc. Michigan USA. 313 pp.

Biological Monitoring of Toxic Metals (1988). Clarkson TW, Friberg L, Nordberg GF and Sager PR (eds.). Plenum Press. New York and London. 686 pp.

Intentionally blank

Abbreviations

AAS	Atomic Absorption Spectrometry
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
AMIS	Air Monitoring Information System
ANOVA	Analysis of variance
ATSDR	Agency for Toxic Substances and Disease Registry, USA
BCR	Community Bureau of Reference (Belgium)
CEC	Commission for Environmental Cooperation
CNS	Central Nervous System
COMAR	Database for certified reference materials, Germany
CUSUM	Cumulative Sum
CV	Coefficient of Variation
DDE	Dichloro-bis-chlorophenylethylene
DDT	Dichlorodiphenyltrichloroethane
DEQAS	Danish External Quality Assessment Schemes
DNA	Deoxyribonucleic acid
EHC	Environmental Health Criteria
EQAS	External Quality Assessment Schemes
EQC	External Quality Control
EtO	Ethylene Oxide
ETS	Environmental Tobacco Smoke
FAO	Food and Agricultural Organization, UN
FEF	Forced Expiratory Flow
FIOH	Finnish Institute of Occupational Health
GDR	German Democratic Republic
GEENET	Global Environmental Epidemiology Network
GEMS	Global Environment Monitoring System
GerES	German Environmental Surveys
GFR	Glomerular Filtration Rate
GFR	German Federal Republic
GIS	Geographic Information Systems
GLOBOCAN	IARC Cancer database, France
HEAL	Human Exposure Assessment Location
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
ICP-AES	Inductively Coupled Plasma - Atomic Emission Spectrometry
ICP-MS	Inductively Coupled Plasma - Mass Spectrometry

IPCS	International Programme on Chemical Safety
IQ	Intelligence Quotient
IQC	Internal Quality Control
ISEA	International Society of Exposure Analysis
ISEE	International Society for Environmental Epidemiology
IUPAC	International Union of Pure and Applied Chemistry
JEM	Job Exposure Matrices
LDL	Low density lipid
MIC	Methyl-isocyanate
MJ	Mega Joule
MW	Molecular weight
NAAQMS	National Ambient Air Quality Monitoring Standards, USA
NAG	N-Acetyl- β -D-glucosaminidase
NIES	National Institute for Environmental Studies, Japan
NIST	National Institute of Standards and Technology, USA
NOEL	No Observed Effect Level
NRC	National Research Council, USA
OCR	Optical Character Recognition
PAH	Polychlorinated aromatic hydrocarbons
PBPK	Physiologically Based Pharmacokinetic
PCB	Polychlorinated Biphenyls
PCP	Phentachlorphenol
PIN	Personal Identification Number
PTEAM	Particle Total Exposure Assessment Methodology
PTWI	Provisional Tolerable Weekly Intake
QA	Quality Assurance
QC	Quality Control
RSPM	Respirable Suspended Particulate Matter
SAHSU	Small Area Health Statistics Unit
SMR	Standard Mortality Ratios
SPM	Suspended Particulate Matter
TLV	Threshold Limit Value
TSP	Total Suspended Particulate
UN	United Nations
UNCED	United Nations Conference on Environment and Development
UNEP	United Nations Environment Programme
US EPA	United States Environmental Protection Agency
WHO	World Health Organization
VOC	Volatile Organic Compounds

Index

A

absorption barriers	16
acceptable daily intake, ADI	47
accuracy	109
acetaldehyde	4
adducts	86
adsorption coefficient	20
air quality standards	73
allergens	78
alpha-2-microglobulin	88
aluminium	165
analysis of variance	120
anecdotal studies	55
arsenic	38, 151, 165
asbestos	4
atomic absorption spectrometry, AAS	166
azarcon	142

B

barium	165
benzene	4
beta-2-microglobulin	87
bias	
constant bias	111
negative bias	111
positive bias	111
proportional bias	110
selection bias	60, 66
bioavailability	76
biological agents	13
biological half-time	27, 39
biological monitoring	6, 40, 51, 85
biomarkers	13, 46, 51, 85
bismuth	151
box plot	118

C

cadmium	8, 30, 39, 165
caesium	76
calcium	165
carbaryl	157
carbon disulphide	4
carbon monoxide	2
carboxyhaemoglobin levels	79
cardiovascular disease	4
case-control study	41
ceruloplasmin	90
chlorination	75
cholesterol	90
cholinesterase inhibitors	146, 148
chromium	152, 165
cobalt	91
coefficient of variation	113
cohort studies	38
comprehensive studies	55
confidence interval	121
confounder	29
control charts	105
copper	88, 165
cotinine	79, 165
creatinine	88, 89
cross-sectional studies	42
cumulative exposure	16, 40

D

DDT	49
definitive method	112
descriptive statistics	116, 117
direct methods	51
dose	16, 21
absorbed dose	21
biologically effective dose	21
dose-effect relationship	23
dose-response relationship	23
target organ dose	21
duplicate samples	113

E

ecological studies	42
effect modifier	29
emission sources	18
environmental	
environment-health chain	18
environmental concentration	16
Environmental Health Criteria, EHC	171
enzyme polymorphism	86
errors	60
ethics committee	123
ethylene oxide	32
exposure	15
current exposure	36, 42
exposure concentration	16
exposure distributions	32
exposure duration	25
exposure factors	16
exposure media	21
exposure pathway	20
exposure route	20
exposure settings	27
exposure-effect relationship	23
exposure-response relationship	23
endogenous exposure	86
frequency of exposure	25
historical exposure	36, 49
long-term exposure	16
modelled exposure	12
prenatal exposure	4
retrospective exposure	36, 39, 41, 152
short-term exposure	16
surrogate exposure variable	57
total exposure assessment	52
extrapolation	12, 63, 95

F

fluoride	29
formaldehyde	80, 164

G

gas chromatography, GC	166
glomerular filtration rate	87
guidelines and standards	5

H

half-time	27, 39, 90, 91
halogenated dioxins	91
hazard identification	45
hazard characterisation	45
heavy metals	163
high-risk groups	32, 53
histogram	119

I

imazalil	147
informed consent	123
in vivo neutron activation	85
indirect methods	51
indoor sources	11
inter-laboratory comparisons	102
interval data	115

J

job-exposure matrix	40
---------------------	----

L

lead	7, 9, 20, 31, 139, 151, 165
level of confidence	56
life-style factors	29
lindane	167
linear regression analysis	103, 120
London cholera study	98
London fog episode	3
low density lipid	90
lung cancer	99, 152

M

magnesium	165
mass spectrometry	166
median	119
mercury	4, 165
metals	4
methyl-isocyanate	157
methylmercury	4
microenvironment	27
Minamata Disease	3
mis-classification	39, 41, 60, 121
modelled data	12
mortality rate	42
multimedia element	9

N

neurological symptoms	4
nickel	82, 151
nicotine	79, 165
nitrate	165
nitrite	165
nitrogen dioxide	11
nitrogen oxides	7
No-Observed-Effect-Level, NOEL	46
nominal data	115
non-parametric methods	116
nutritional status	30

O

occupational standard	5
oesophagus cancer	82
ordinal data	115
organic solvents	6
organochlorine contaminants	94
osteofluorosis	29
outliers	109
ozone	73

P

parametric methods	116
paraquat	148
peak exposure	26
pentachlorophenol, PCP	167
percentiles	119
personal monitors	4
pesticides	6, 145
petrol	9
pharmacokinetic parameters	91
phosphorous	165
physical activity	32
physical agents	13
physiologically based pharmacokinetic, PBPK	95
pica	84
pilot study	59
polychlorinated biphenyls, PCB	20, 31, 76
power calculations	55
precision	109, 113
primary urine	87
probability sample study	55
prospective study	38
psychomotor retardation	4

Q

quality assurance, QA	101
quality control, QC	101

R

radon	4
Ramazzini, Bernardino	2
random variation	111
range	119
reference method	112
regression analysis	120
representative sample	55
retrospective study	38
risk characterisation	47
risk communication	44

S

sampler	133
active sampler	79
high-volume sampler	133
passive sampler	80, 165
personal sampler	79, 165
sample size	55
sample variance (s^2)	119
selenium	151
semi-individual	43
sensitivity analysis	121
sevin	157
Shewhart chart	105
Snow, John	2
socio-economic factors	30
soot	4
specific gravity	88, 89
specimen bank	49, 86, 125
standard deviation, SD	119
steady state	91
strontium	165
sulphur dioxide	3, 151
surrogate	37, 39, 57, 73, 80
survey	55
susceptibel groups	32
suspended particulate matter, SPM	129

T

tellurium	152
thermoluminescent detector	85
thiabendazole	147
time	25
time-activity data	27, 69, 97
time-activity diaries	51
time-activity pattern	27, 65, 69
time-series studies	43
time-weighted integrated exposure model	97
topical lesions	148
toxicokinetics	22
transferrin	90

transformation of pollutants	18
transport of pollutants	18
tubular proteinuria	38

V

variations	
day-to-day	28
seasonal	49
volatile organic compounds, VOC	164

X

x-ray fluorescence	86
--------------------	----

Z

zinc	88, 165
------	---------

References

Armstrong BK, White E and Saracci R (1992) Principles of exposure measurement in epidemiology. Oxford University Press, Oxford, England.

Aylin P, Maheswaran R, Wakefield J, Cockings S, Jarup L, Arnold R, Wheeler G, Elliott P (1999) A national facility for small area disease mapping and rapid initial assessment of apparent disease clusters around a point source: the UK Small Area Health Statistics Unit. *J Public Health Med* 21(3):289-298.

Baer R, Ackerman A (1988) Toxic Mexican folk remedies for the treatment of empacho: the case of azarcon, greta, and albayalde. *J Ethnopharmacol* 24:29-31.

Baker D, Kjellström T, Calderon R, Pastides H, eds. (1999) Environmental Epidemiology. A Textbook on Study Methods and Public Applications. WHO/SDE/OEH/99.7. Preliminary Edition. World Health Organization and United States Environmental Protection Agency. World Health Organization, Geneva. 342 pp.

Bakir F, Damluji SF, Amin-Zaki L, Murtadha M, Khalidi A, al-Rawi NY, Tikriti S, Dahahir HI, Clarkson TW, Smith JC, Doherty RA (1973) Methylmercury poisoning in Iraq. *Science* 181(96):230-241.

Beaglehole R, Bonita R, Kjellström T (1993) Basic epidemiology. World Health Organization, Geneva. 175 pp.

Berglund M, Åkesson A, Nermell B, Vahter M (1994a) Intestinal absorption of dietary cadmium in women is dependent on body iron stores and fiber intake. *Environ Health Perspec* 102:1058-1066.

Berglund M, Bråbäck L, Bylin G, Jonson J-O, Vahter M (1994b) Personal NO₂ exposure monitoring shows high exposure among ice-skating schoolchildren. *Arch Environ Health* 49(1):17-24.

Briggs D, Corvalán C, Nurminen M, eds. (1996) Linkage Methods for Environment and Health Analysis. General guidelines. A report for the Health and Environment Analysis for Decision-making (HEADLAMP) project. United Nations Environment Programme, United States Environmental Protection Agency, Office of Global and Integrated Environmental Health, World Health Organization, Geneva. WHO/EHG/95.26. 136 pp.

Buchet J, Lauwerys R, Roels H, Bernard A, Bruaux P, Claeys F, Ducoffre G, De Plaen P, Staessen J, Amery A, Lijnen P, Thijs L, Rondia D, Sartor F, Saint Remy A, Nick L (1990). Renal effects of cadmium body burden of the general population. *Lancet* 336:699-702.

Burke T, Anderson H, Beach N, Colome S, Drew RT, Firestone M, Hauchman FS, Miller TO, Wagener DK, Zeise L, Tran N (1992) Role of exposure databases in risk management. *Arch Environ Health* 47(6):421-429.

Calabrese EJ, Barnes R, Stanek E, Pastides H, Gilbert CE, Veneman P, Wang X, Lasztity A and Kostecki PT (1989) How much soil do young children ingest: an epidemiologic study. *Reg Toxic Pharm* 10:123-137.

Callahan MA, Clickner RP, Whitmore RW, Kalton G, Sexton K (1995) Overview of important design issues for a national human exposure assessment survey. *J Exp Anal Environ Epidemiol* 5(3):257-282.

Chaverri F, Blanco J (1995) Importacion, formulacion y uso de plaguicidas en Costa Rica. Período 1992-1993. Informe final al proyecto MASICA/OPS. Programa de Plaguicidas, Universidad Nacional, Heredia, Costa Rica. (In Spanish).

Checkoway H, Pearce N, Crawford-Brown DJ (1989) Research Methods in Occupational Epidemiology. Monographs in Epidemiology and Biostatistics. Volume 13. Oxford University Press, New York, Oxford.

Commission of the European Communities (1993) European Collaborative Action of Indoor Air Quality & its Impact on Man. Report No. 12, Biological particles in indoor environments. ECSE-EEC-EAEC, Brussels-Luxembourg.

Contreras R (1990) Gasolinas de alto octanaje; con bajo contenido de plomo y azufre. *Rev Mex Hig segur*, December:14-17. (In Spanish).

Cooper DB (1980) Plomo epidemias en la Ciudad de Mexico 1761-1813. Coleccion Salud y Seguridad Social. Serie Historia. Mexico City: Instituto Mexicano del Seguro Social. (In Spanish).

Cullinan P, Acquilla S, Ramana Dhara V (1997) On behalf of the International Medical Commission on Bhopal. Respiratory morbidity 10 years after the Union Carbide gas leak at Bhopal: a cross sectional survey. *BMJ* 314:338-342.

Dreborg S, Einarsson R, Lau S, Munir AKM, Wahn U (1995) Dust sampling for determination of allergen content. *Allergy* 50:188-189.

Dobbs AJ, Hunt DET (1991) Sampling and analysis of water to assess exposure. In: *Methods for Assessing Exposure of Human and Non-human Biota*. Scope 46. Tardiff RG, Goldstein BD (eds.). IPCS Joint Symposia 13, SGOMSEC 5. John Wiley & Sons, Chichester, England, pp. 219-232.

Dockery DW, Pope III CA (1994) Acute respiratory effects of particulate air pollution. *Annu Rev Public Health* 15:107-132.

Dockery DW, Pope III CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG and Speizer FE (1993) An association between air pollution and mortality in six U.S. cities. *New Engl J Med* 329:1753-1759.

Doll R, Peto R (1978) Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *J Epidemiol & Community Health* 32(4):303-313.

Duan N (1982) Models for human exposure to air pollution. *Environ Int* 8:305-309.

Elinder C-G, Friberg L, Nordberg G F, Kjellström T, Oberdoerster G (1994) Biological Monitoring of Metals. Chemical safety monographs. International Programme on Chemical Safety. WHO/EHG/94.2. 80 pp.

Elliott P, Wakefield JC, Best NG, Briggs D, eds. (2000) *Spatial Epidemiology: Methods and Applications*, Oxford University Press, Oxford, UK.

Enterline P (1976) Pitfalls in epidemiological research. *J Occup Med* 11:513-521.

FAO/WHO (1984a) *The Role of Food Safety in Health and Development*. Report of a joint FAO/WHO Expert Committee on Food Safety. WHO Technical Report Ser. No. 705. Food and Agricultural Organization, World Health Organisation, Geneva. 52 pp.

FAO/WHO (1984b) *CODEX Alimentary Norms for Fruit Juices, Juice of Concentrated Fruits and Nectar of Fruits*, vol. 10, 1st ed. Rome, Food and Agricultural Organization, World Health Organisation.

Gheorghiev G K (1991) Monitoring systems for the assessment of dietary intakes of contaminants. In: *Methods for Assessing Exposure of Human and Non-human Biota*. Scope 46. Tardiff RG, Goldstein BD (eds.). IPCS Joint Symposia 13, SGOMSEC 5. John Wiley & Sons, Chichester, England, pp. 233-248.

Graham J, Walker KD, Berry M, Bryan EF, Callahan MA, Fan A, Finley B, Lynch J, McCone T, Ozkaynak H, Sexton K (1992) Role of exposure databases in risk assessment. *Arch Environ Health* 47(6):408-420.

GTRI (1992) *Lead-based paint detection and abatement*. Georgia Technical Research Institute, Environmental Sciences and Technology Laboratory, Atlanta, Georgia.

Hallberg L, Hultén L, Lindstedt G, Lundberg PA, Mark A, Puren J, Svanberg B, Swolin B (1993) Prevalence of iron deficiency in Swedish adolescents. *Pediatric Res* 34(5):680-687.

Hassler E (1983) *Exposure to cadmium and nickel in an alkaline battery factory - as evaluated from measurements in air and biological material*. Doctoral thesis, Department of Environmental Hygiene, Karolinska Institute, Stockholm, Sweden. 227 pp.

Heinzow BG, McLean A (1994) Critical evaluation of current concepts in exposure assessment. *Clin Chem* 40:1368-1375.

Hernandez-Avila M, Romieu I, Rios C, Rivero A, Palazuelos E (1991) Lead-glazed ceramics as major determinants of blood lead levels in Mexican women. *Environ Health Perspect* 94:117-120.

Hill SB (1965) The environment and disease: Association or causation. *Proc Royal Soc Med* 58:295-300.

IAEA (1995) Survey of reference materials. Volume 1: Biological and Environmental Reference Materials for Trace Elements, Nuclides and Microcontaminants. IAEA-TECDOC-854. International Atomic Energy Agency and United Nations Environment Programme, Vienna, Austria.

IAEA (1996) Survey of reference materials. Volume 2: Environmentally Related Reference Materials for Trace Elements, Nuclides and Microcontaminants. IAEA-TECDOC- 880. International Atomic Energy Agency and United Nations Environment Programme, Vienna, Austria.

Jacobson JL, Jacobson SW (1996) Intellectual impairment in children exposed to polychlorinated biphenyls in utero. *N Eng J Med* 335:783-789.

Jeyaratnam J (1990) Acute pesticide poisoning: a major global health problem. *Wld Hlth Statist Quart* 43:139-144.

Jorhem L, Slorach S (1988) Design and use of quality control samples in a collaborative study of trace metals in daily diets. *Fresenius Z Anal Chem* 332:738-740.

Järup L (1992) Dose-response relations for occupational exposure to arsenic and cadmium. Doctoral thesis, Department of Environmental Hygiene and Institute of Environmental Medicine, Department of Epidemiology, Karolinska Institute and Department of Occupational Medicine, Karolinska Hospital, Stockholm, Sweden.

Järup L, Elinder CG (1994) Dose-response relations between urinary cadmium and tubular proteinuria in cadmium-exposed workers. *Am J Ind Med* 26(6):759-769.

Järup L, Pershagen G (1991) Arsenic exposure, smoking, and lung cancer in smelter workers - a case-control study. *Am J Epidemiol* 134:545-51.

Järup L, Elinder CG, Spång G (1988) Cumulative blood-cadmium and tubular proteinuria: a dose-response relationship. *Int Arch Occup Environ Health* 60:223-229.

Järup L, Pershagen G, Wall S (1989) Cumulative arsenic exposure and lung cancer in smelter workers: A dose-response study. *Am J Ind Med* 15:31-41.

Kalton G (1983) Introduction to survey sampling. Saga University Paper series on Quantitative Applications in the Social Sciences, 35. Saga Publications, Inc., Beverly Hills and London.

Kollander M (1993) Guidance on survey design for Human Exposure Assessment Location (HEAL) studies. World Health Organization, Geneva. WHO/PEP/92.6.

Künzli N, Tager IB (1997) The semi-individual study in air pollution epidemiology: A valid design as compared to ecologic studies. *Environ Health Perspect* 105:1078-1083.

Langworth S, Elinder CG, Sundquist KG, Vesterberg O (1992) Renal and immunological effects of occupational exposure to inorganic mercury. *Br J Ind Med* 49(6):394-401.

Lauwerys R, Hoet P (1993) Industrial Chemical Exposure. Guidelines for Biological Monitoring. Second ed. Lewis Publishers. Boca Raton, Ann Arbor, London, Tokyo. 313 pp.

Lee ES, Frothoefner RN, Lorimor RJ (1989) Analyzing complex survey data. Quantitative applications in the social sciences, No. 171. Sage University Paper series, Newbury Park.

Lind B, Vahter M, Rahnster B, Björs U (1988) Quality control samples for the determination of lead and cadmium in blood, feces, air filters, and dust. *Fresenius Z Anal Chem* 332:741-743.

Linkage Methods for Environment and Health Analysis. General Guidelines. A Report of the Health and Environment Analysis for Decision-making (HEADLAMP) Project (1996). Edited by Briggs D, Corvalán C and Nurminen M. WHO/EHG/95.26. World Health Organization, Geneva. 136 pp.

Linkage Methods for Environment and Health Analysis. Technical Guidelines (1997). Edited by Corvalán C, Nurminen M and Pastides H. WHO/EHG/97.11. World Health Organization, Geneva. 153 pp.

Lioy PJ (1990) Assessing total human exposure to contaminants. *Environ Sci Technol* 24(7):938-945.

Lundén Å, Norén K (1998) Polychlorinated Naphtalenes and other Organochlorine Contaminants in Swedish Human Milk, 1972-1992. *Arch Environ Contam Toxicol* 34:414-423.

Lwanga SK, Lemeshow S (1991) Sample Size Determination in Health Studies. A practical manual. World Health Organization, Geneva. 80 pp.

Masters GM (1991) Introduction to Environmental Engineering and Science. Reinhold, New York.

McKone TE, Daniels JI (1991) Estimating human exposure through multiple pathways from air, water, and soil. *Regul Toxicol Pharmacol* 13(1):36-61.

NRC (1983) Risk Assessment in the Federal Government: Managing the process. National Research Council, National Academy Press, Washington D.C., USA.

NRC (1991a) Frontiers in Assessing Human Exposures to Environmental Toxicants. National Research Council, National Academy Press, Washington D.C., USA.

NRC (1991b) Human Exposure Assessment for Airborne Pollutants. Advances and Opportunities. National Research Council, National Academy Press, Washington, D.C., USA. 321 pp.

NRC (1993) Measuring Lead Exposure in Infants, Children, and Other Sensitive Populations. National Research Council, National Academy Press, Washington D.C., USA. 337 pp.

Nurminen M, Hernberg S (1985) Effects of intervention on the cardiovascular mortality of workers exposed to carbon disulphide: a 15 year follow up. *Br J Ind Med* 42:32-35.

Nyberg F, Gustavsson P, Järup L, Bellander T, Berglind N, Jakobsson R, Pershagen G (2000) Urban Air Pollution and Lung Cancer in Stockholm. *Epidemiology* 11:587-595.

Ozkaynak H, Xue J, Spengler JD, Wallace L, Pellizzari E, Jenkins P (1996) Personal exposure to airborne particles and metals: results from the particle TEAM study in Riverside, California. *J Expo Anal Environ Epi* 6(1):57-78.

Prichard E (1995) Quality in the Analytical Chemistry Laboratory. John Wiley & Sons Ltd, Chichester, England. 307 pp.

Risk Assessment and Toxicology Steering Committee (1999) Risk assessment approaches used by UK Government for evaluating human health effects of chemicals. The Institute for Environmental Health, Leicester, UK.

Rodríguez AC, Ahlbom A, Wesseling C (1995) A surveillance system for pesticide poisonings, Cariari, Costa Rica. *Epidemiology* 6(4 Suppl):S122.

Romieu I, Palazuelos E, Hernandez Avila H, Rios C, Muños I, Jimienez C, Cahero G (1994) Sources of lead exposure in Mexico City. *Environ Health Perspect* 102:384-389.

Romeiu I, Carreon T, Lopez L, Palazuelos E, Rios C, Manuel Y, Hernandez Avila H (1995) Environmental urban lead exposure and blood lead levels in children of Mexico City. *Environ Health Perspect* 103:1036-1040.

Sanchez C (1990) Analisis temporal del plomo atmosferico en el area metropolitana de la Ciudad de Mexico durante el periodo 1984-1989. Presentation at the National Lead Meeting, Mexico City, Mexico. (In Spanish).

Sexton K, Selevan SG, Wagener DK, Lybarger JA (1992) Estimating human exposures to environmental pollutants: Availability and utility of existing databases. *Arch Environ Health* 47(6):398-407.

Sexton K, Callahan MA, Bryan EF, Saint CG, Wood WP (1995) Informed decisions about protecting and promoting public health: Rationale for a national human exposure assessment survey. *J Expo Anal Environ Epi* 5(3):233-256.

Schulte PA, Sweeney MH (1995) Ethical considerations, confidentiality issues, rights of human subjects, and use of monitoring data in research and regulation. *Environ Health Perspect* 3:69-74.

Skare I, Enquist A (1994) Human exposure to mercury and silver released from dental amalgam restorations. *Arch Environ Health* 49:384-394.

Soskolne C, Light A (1996) Towards ethics guidelines for environmental epidemiologists. *Sci Tot Environ* 1,2:137-147.

Strömberg U, Schütz A, Skerfving S (1995) Substantial decrease of blood lead in Swedish children, 1978-94, associated with petrol lead. *Occup Environ Med* 52:764-769.

Taylor A, Patriarca M, Menditto A, Morisi G (1996) Prospects of harmonisation of European external quality assessment schemes in occupational and environmental laboratory medicine. *Ann Ist Super Sanità* 32(2):295-307.

Thomas VM, Socolow RH, Fanelli JJ, Spiro TG (1999) Effects of reducing lead in gasoline: An analysis of the international experience. *Environ Sci & Technol* 33(22):3942-3948.

Tsubaki T, Irukayama K, eds. (1977) *Minamata Disease*. Kodansha Ltd., Tokyo, Elsevier, Amsterdam.

UNEP (1992) A survey of organizations and laboratories manufacturing, supplying or using reference materials for environmental measurement. Delve M, Mandry P (eds.). draft edition, November 1992, United Nations Environment Programme, Harmonization of Environmental Measurement (HEM) office, Munich, Germany. 131 pp.

UNEP/WHO (1986) Human Exposure Assessment Location HEAL Project. Guidelines for Integrated Air, Water, Food and Biological Monitoring. United Nations Environment Programme and the World Health Organization, Geneva, PEP/86.6. 315 pp.

United Kingdom Ministry of Health (1954) Mortality and Morbidity During the London Fog of December 1952. London, Her Majesty's Stationery Office.

US EPA (1992) Guidelines for Exposure Assessment. Federal Register, Vol 57, No.104. United States Environmental Protection Agency, Washington, D.C., USA.

US EPA (1997) Exposure Factors Handbook. EPA/600/P-95/002Fa. United States Environmental Protection Agency, Washington DC., USA.

Vahter M, Berglund M, Slorach S, Friberg L, Saric M, Xingquan Z, Fujita M (1991) Methods for integrated exposure monitoring of lead and cadmium. Environ Res 56:78-89.

Vahter M, Berglund M, Nermell B, Åkesson A (1996) Bioavailability of cadmium from shellfish and mixed diet in women. Toxicol Appl Pharmacol 136:332-341.

van Wendel de Joode BN, de Graaf IA, Wesseling C, Kromhout H (1996) Paraquat exposure of knapsack applicators on banana plantations in Costa Rica. Int J Occup Environ Health 2(4):294-304.

Vaquerano BD (1995) Caracterizacion de la exposicion dermal ocupacional a plaguicidas en una finca bananera en Costa Rica, 1995. Tesis para grado de Magister Scientiae en Salud Publica, Universidad de Costa Rica. (In Spanish).

Wesseling C, Castillo L, Elinder CG (1993) Pesticide poisonings in Costa Rica. Scand J Work Environ Health 19:227-35.

Wesseling C, Ahlbom A, Antich D, Rodriguez AC, Castro R (1996) Cancer in banana plantation workers in Costa Rica. *Int J Epidemiol* 25(6):1125-1131.

Wesseling C (1997) Health effects from pesticide use in Costa Rica: an epidemiologic approach. Doctoral thesis, Karolinska Institutet, National Institute for Working Life, Stockholm.

Wesseling C, Hogstedt C, Picado A, Johansson L (1997) Unintentional fatal paraquat poisonings among agricultural workers in Costa Rica: report of fifteen cases. *Am J Ind Med* 32(5):433-441.

Wesseling C, van Wendel de Joode B, Monge P (2001) Pesticide-related illness among banana workers in Costa Rica: A comparison between 1993 and 1996. *Int J Occup Environ Health*. (*In press*)

WHO (1982) Estimating human exposure to air pollutants. World Health Organization, Geneva.

WHO (1984) Principles and Procedures for Quality Assurance in Environmental Pollution Exposure Monitoring. EFP/HEAL/84.4, World Health Organization, Geneva.

WHO (1985) Guidelines for the Study of Dietary Intakes of Chemical Contaminants. Publication No: 87, World Health Organization, Geneva. 102 pp.

WHO (1995) Inorganic lead. Environmental Health Criteria 165. International Programme on Chemical Safety, World Health Organization, Geneva, 300 pp.

WHO (1993) Guidelines for Drinking-water Quality. Vol 1: Recommendations. World Health Organization, Geneva.

WHO (1996a) Guidelines for Drinking-Water Quality, Vol 2: Health Criteria and Other Supporting Information. World Health Organization, Geneva.

WHO (1998a) Guidelines for Drinking-Water Quality. Addendum to Volume 1: Recommendations. World Health Organization, Geneva.

WHO (1998b) Guidelines for Drinking-Water Quality. Addendum to Volume 2: Health Criteria and Other Supporting Information. World Health Organization, Geneva.

WHO (1996b) World Health Organization Meeting Report. Joint WHO-ISEE International Workshop on Ethical and Philosophical Issues in Environmental Epidemiology, Research Triangle Park, North Carolina, U.S.A., September 16-18, 1994. *Sci Tot Environ* 1-2:131-136.

WHO (1999) Air Quality Guidelines. Second edition. World Health Organization, Geneva. In press. The document can be accessed from the WHO web site.

Åkesson A, Berglund M, Schütz A, Bjellerup P, Bremme K, Vahter M (2002) Cadmium exposure in pregnancy and lactation in relation to iron status. *Am J Public Health* 92: 284-287.

Åstrand I (1983) Effect of physical exercise on uptake, distribution and elimination of vapors in man. In: Fiseroca-Bergerova V (ed). *Modeling of Inhalation Exposure to Vapors: Uptake, Distribution, and Elimination*. CRC Press, vol II, pp. 107-130.