RISK OF CONGENITAL ANOMALY IN RELATION TO RESIDENCE NEAR HAZARDOUS WASTE LANDFILL SITES

by

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Thesis submitted to the University of London for the degree of Doctor of Philosophy

London School of Hygiene and Tropical Medicine

2000

Abstract

The main aim of this thesis is to investigate whether residence near hazardous waste landfill sites is associated with an increased risk of congenital anomaly. The thesis reports results of a multi-centre case-control study carried out in 10 regions in 6 European countries. Cases were live births, stillbirths, and induced abortions with major congenital anomalies resident at birth within a 7 km area around hazardous waste landfill sites. Controls, two per case, were non-malformed births resident in the same area. A total of 1089 cases of non-chromosomal anomaly, 270 cases of chromosomal anomaly, and 2508 controls were selected around 26 landfill sites. A 3 km zone around sites was defined as the zone of most likely exposure. An expert panel of four landfill specialists scored each landfill site according to their potential to cause exposure of nearby residents. A statistically significant 33% excess in risk of non-chromosomal anomalies was found for living within 3 km of a hazardous waste landfill site. The risk of non-chromosomal anomaly declined steadily with increasing distance from a site. Confounding factors or biases do not readily explain these findings. Risk of chromosomal anomalies was raised near sites but did not reach statistical significance. There was little evidence for relative risk of congenital anomaly (non-chromosomal or chromosomal) close to landfill sites to be associated with hazard potential of landfill sites, adding little support to a possible causal relationship. However, in the absence of a 'gold-standard' for the classification of hazard potential, misclassification of sites may have occurred. Lack of information on exposure of residents near the study sites or near landfill sites in general, limits interpretation of the results. Socio-economic status is a potential confounding factor in the current study but little is known in the literature about socio-economic status as a risk factor for congenital anomaly. This study finds a higher risk of non-chromosomal congenital anomaly and certain specific malformation groups in more deprived populations. These findings require follow-up in studies with larger geographical coverage.

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ACKNOWLEDGEMENTS

The work described in this thesis was possible only through the involvement of a great number of people and institutions.

First of all I would like to thank Helen Dolk for her supervision and for being very supportive and encouraging of my work in general. Her precise and critical attitude were essential to this research and I hope I have learned from this. Even more, I appreciate her friendly character and hope our collaboration will continue. Ben Armstrong was my supervisor during Helen's absence and has advised me on the statistical analysis and interpretation of results. Thanks Ben, I feel hugely privileged for having received input from not just one but two such excellent and friendly supervisors. I also thank the other members of my advisory committee, Tony Fletcher and Frank Sullivan, for valuable advice at crucial stages in the PhD.

The EUROHAZCON study was the work of many individuals. First of all Helen Dolk was the principal investigator of the study and supervised all parts of the study. Ben Armstrong supervised the statistical analyses. Lenore Abramsky, Eva Alberman, Fabrizio Bianchi, Ester Garne, Vera Nelen, Elisabeth Robert, John Scott, David Stone, and Romano Tenconi took part in study protocol design, advised on the classification of cases, and supplied data from the participating centres. Members of the expert panel, Giorgio Boschi, Torben Jorgensen, Calum MacDonald, and Patrick Pointer, played a major role in development of the ranking questionnaire and the hazard potential classification. I am grateful also to the other local landfill specialists who provided information about the sites in their local areas and filled in the landfill questionnaires: Michael Fogh, Tom McDonald, Isabel Melkebe, Marco Pellegrini, Fabio Del Soldato and staff at Réseau Santé-Déchet. I thank Peter Egger and Bharat Thakar for their help in running and interpreting some of the statistical programmes used in data analyses, and Celi Busby for her help in the beginning stages of the hazard potential ranking exercise.

The EUROHAZCON study was funded by the European BIOMED programme. I am very grateful to my sponsors The Colt Foundation for providing additional funding for the completion of my PhD in the form of a Research Fellowship. The literature review on health effects of landfill sites was specifically funded by the Environment Agency North-West Region.

Last but not least I would like to thank all colleagues and ex-colleagues of the Environmental Epidemiology Unit for providing such a very warm and friendly working environment. I have made many good friends here. Special thanks to Celi Busby and Megan Landon for being such supportive room mates and friends for many years : I hope I have learned something from your 'nappy conversations'. Celi, thanks also for proof reading some of my chapters.

CHAPTER 1

INTRODUCTION

1.1 HAZARDOUS WASTE LANDFILL SITES

Industrial societies produce increasingly large volumes of waste, including wastes of potentially toxic nature. It is estimated that the United States (U.S.) generate more than 6 billion tonnes of waste every year and European Union countries around 2.5 billion tonnes (Brand, 1993; National Research Council, 1991). The most common method of disposing of waste has been and still is in many countries the deposition of waste in landfill sites. Landfill sites can in common terms be described as 'holes in the ground' specifically allocated for the purposes of waste disposal (British Medical Association, 1991; Westlake, 1995). Landfill sites are numerous and widespread in Europe and elsewhere, although it is difficult to estimate total numbers of sites due to the unknown location of many old and illegal dumps. It is estimated that in the United Kingdom (U.K.) around 70% of all waste is disposed of in landfill sites (Department of the Environment, 1995). Table 1.1 shows that the extent to which landfill is used as a disposal method varies considerably between European countries. The U.K. for example, relies more heavily on landfill than most other European countries where treatment and incineration of waste are increasingly important disposal methods.

Table 1.1: Hazardous waste disposal methods in selected European countries (from Brand, 1993)

	Belgium	*Denmark*	*France*	*Germany*	*U.K.*	*Netherlands*
Incineration						
facilities (number)	1	1	25	17	4	7
capacity (tonnes)	40	90	600	620	80	160
Physical/chemical treatment						
facilities (number)	1	1	10	23	13	6
capacity (tonnes)	24	20	300	280	?	30
Landfill						
facilities (number)	4	1	12	22	1200	?
capacity (tonnes)	?	?	500	2250	2290	20

An estimated one percent of the total of 2.5 billion tonnes of waste produced in the European Union annually has been defined as 'hazardous' (Brand, 1993). It is difficult to

define which wastes are 'hazardous', as will be discussed in further chapters of this thesis. As a general definition, hazardous wastes have been defined as wastes which "have the potential to cause harm to human health and the environment if they are improperly treated, stored, transported, or inadequately disposed of" (British Medical Association, 1991).

Information about the types and amounts of hazardous substances deposited in landfills, or potentially being emitted from landfills, is usually poor. The presence of landfills containing mixtures of unknown but potentially hazardous chemicals in unknown quantities nearby residential populations, has caused increasing public concern about possible health effects. One of the earliest and most well-known examples of a waste site prompting extensive concern from the public is Love Canal, New York State. Large quantities of toxic materials (residues from pesticide production) were dumped at Love Canal in the forties and fifties, followed by the building of houses and a school on and around the waste site. In the seventies the site was leaking and residents were evacuated. Similar events in the Dutch town of Lekkerkerk led to evacuation of residents in 1981 (British Medical Association, 1991). More recently, public concerns and reports of clusters of adverse health effects have led to site investigations and health studies in several European countries, including sites located in Mellery, Belgium, Montchanin in France, North-Rhine Westfalia, Germany, and Nant-y-Gwyddon, Wales (Fielder et al, 1998; Greiser et al, 1991; Lakhanisky et al, 1993; Zmirou et al, 1994). Waste disposal features high on lists of most important environmental concerns for the public in the U.K. (British Medical Association, 1991) and elsewhere (Baxter, 1990).

Despite widespread public concern and media attention there is as yet no full understanding of the extent to which the public may be exposed to substances present at landfill sites, if at all, the substances to which they may be exposed, the pathways of exposure, or the potential health effects associated with such exposure. Exposure to landfill site contamination is difficult to measure. These issues will discussed in depth in the following chapters of this thesis.

1.2 CONGENITAL ANOMALIES

The terms 'congenital anomalies', 'birth defects', and 'congenital malformations' are all used to describe developmental defects that are present at birth. The term anomaly is commonly used for all types of structural defects, chromosomal abnormalities, genetic syndromes, and metabolic defects (Dolk and de Wals, 1992; EUROCAT Working Group, 1997; Kline et al,

1989). Some authors include functional and behavioural defects present at birth within the term congenital anomaly (Moore and Persaud, 1993; Persaud, 1985). Classifications of structural defects have been proposed which define the term congenital malformations in a stricter sense as "morphological defects of an organ, part of an organ, or larger part of the body as a result of an intrinsically abnormal developmental process" (Moore and Persaud, 1993; Persaud, 1985; Spranger et al, 1982). Malformations are distinguished in this classification from other structural defects, disruption, deformations, and dysplasias, by their "intrinsic nature of defect", meaning that the development of the organ was abnormal from the start, or near the start, of its development (Persaud, 1985; Spranger et al, 1982).

Estimates of the prevalence of congenital anomalies vary between 2 to 6% of births (Persaud, 1985). The prevalence may vary considerably depending on the definition used, criteria used to include or exclude minor malformations, and the time period of follow-up after birth. Major structural congenital anomalies are commonly reported to be present in two to three per cent of births (Persaud, 1985). In EUROCAT (European Network of Congenital Anomaly Registries) centres the prevalence rate of congenital anomalies (including major structural defects, chromosomal abnormalities, some inborn error of metabolism, and genetic syndromes) was 2.3 per cent between 1990 and 1994, varying from 0.99 to 3.61 in individual centres (EUROCAT Working Group, 1997).

Congenital anomalies are a leading cause of infant mortality and an important contributor to childhood and adult morbidity. Persaud (1985) reported that 20% of neonatal deaths could be attributed to major congenital malformations. Statistics from the Office for National Statistics in the U.K. show that in 1995, congenital malformations were the second most frequently recorded cause of neonatal deaths (18%), after prematurity related conditions (31%)(Office for National Statistics, 1997). Indeed, congenital malformations have been reported to account for half of all neonatal deaths in higher birthweight babies (>2,000 grams), and for only 10% of deaths in lower birthweight babies (Winter et al, 1989). Major congenital anomalies in surviving infants often have serious medical and/or cosmetic consequences and commonly require surgery.

The aetiology of congenital anomalies is unknown in more than half of babies affected. Since the thalidomide disaster and the discovery of the congenital rubella syndrome a number of human teratogens (mainly infectious agents and medical drugs) have been discovered but still only a small number of cases can be attributed to environmental causes. In 1983 Kalter and Warkany estimated single environmental causes to account for around 7-10% of major malformations, chromosomal abnormalities for 6-7%, single gene mutations for 7-8%, and

multifactorial inheritance, in which genetic and environmental factors interact to cause malformation, for around 20% (Kalter and Warkany, 1983). Environmental exposures may play a role in chromosomal abnormalities, single gene mutations, cases of multifactorial inheritance cases, and in those that remain of unknown aetiology. Many toxic chemicals have shown in animal experiments to have the potential to affect the development of the embryo and fetus and cause congenital anomalies (further discussed in section 2.3 of this thesis). Landfill sites represent a potential source of exposure to such teratogenic chemicals, although it is not clear whether exposure exceeds threshold doses needed to induce teratogenic effects.

It is likely that clusters of congenital anomalies and other adverse health outcomes near landfill sites will continue to be reported as a reflection of public concerns. The potential hazard posed by landfill sites to the health of nearby residents and their unborn children requires careful evaluation in order to respond to these public concerns in a satisfactory way, and in order to decide on adequate regulation, siting, and remediation of sites.

1.3 AIMS AND OBJECTIVES

The main aim of the thesis is to investigate whether residence near hazardous waste landfill sites is associated with an increased risk of congenital anomaly. The thesis is based on a multi-centre case-control study of risk of congenital malformation in the vicinity of hazardous waste landfill sites (EUROHAZCON) carried out in 10 regions in 6 European countries.

Specific objectives of this thesis are :

1. To review background literature on assessment and ranking of hazards posed by landfill sites, on evidence for human exposure from landfill sites, on teratogenic potential of chemicals present at landfill sites, on adverse health effects related to residence near landfill sites, and on other risk factors for congenital anomalies which may be of relevance to the investigation.
2. To investigate whether congenital anomaly cases tend to live nearer to hazardous waste landfill sites than do controls, allowing for potential confounding of factors such as socio-economic status and maternal age, and to quantify the risk in defined geographic zones based on distance of residence from the landfill sites.

3. To develop a classification of the relative hazard potential of EUROHAZCON study sites according to their likelihood to cause off-site contamination and exposure of residents, in order to identify sites with higher and lower hazard potential.

4. To investigate whether sites classified as posing a greater potential hazard are associated with a greater risk of congenital anomaly in their vicinity. The investigation of such a 'dose-response' effect could provide additional evidence in assessing the likelihood of causality of any relationship between distance of residence from landfill sites and risk of congenital malformation.

5. To investigate the extent of socio-economic variation in risk of congenital anomalies, including specific congenital anomaly groups. Socio-economic status is an important potential confounding factor in the relationship between proximity to landfill sites and risk of congenital anomaly. Little is known however about its role as a risk factor for congenital anomaly. I therefore included a detailed analysis of socio-economic variation in risk of congenital anomalies in this thesis.

The EUROHAZCON study was originally set up because a need was identified for studies investigating landfill sites in Europe defined a-priori, independently from reported clusters of adverse health outcomes. A secondary aim of the project was to develop a framework protocol for multi-centric European studies of congenital malformation in relation to other environmental exposures. Congenital anomalies are rare and pooling of data from different regions and countries is often necessary to achieve sufficient statistical power. A 'statement of conjoint work' attached in Appendix 1 of this thesis describes my role and the role of other collaborators in the EUROHAZCON project. Appendix 2 includes papers published from this research to date.

1.4 THESIS OUTLINE

Chapter 2 of this thesis includes background literature reviews, starting in section 2.1 with a review of factors which determine hazards posed by landfill sites and of existing methods developed to rank landfill sites according to their potential hazard. This section forms important background to classification of the hazard potential of EUROHAZCON sites. Section 2.2 describes current evidence for exposure of residents living near landfill sites to pollution from the landfill sites and includes an assessment of the types of chemicals and concentrations to which residential populations may be exposed. The following section of the literature chapter, section 2.3, describes evidence from both animal and human studies for

teratogenic potential of the main groups of chemicals that may be present in contamination from landfill sites. Section 2.4 reviews the epidemiological literature on health effects of residence near landfill sites, congenital anomalies as well as other health outcomes. Section 2.5 reviews life-style and demographic risk factors for congenital anomalies, in order to assess their potential confounding role in the relationship between residence near landfill sites and risk of congenital anomaly, and as general background to congenital anomaly epidemiology. Specific attention will be paid in this section to socio-economic status as a risk factor for congenital anomalies, this being one of the main thesis objectives.

Chapter 3 describes methods for data collection (3.1-3.5), methods used to measure exposure and classify sites (3.6), and methods used to analyse data (3.7). In chapter 4 I present the results of the study, including basic descriptive information (section 4.1), the relation between distance of residence and risk of congenital anomaly (section 4.2), results of the hazard potential classification (section 4.3), the relationship between hazard potential and risk of congenital anomaly near landfill sites (section 4.4), and an assessment of socio-economic variation in the risk of congenital anomalies (section 4.5). In chapter 5 I evaluate the methodology of the study, discuss the results and their interpretation, and draw conclusions from this research.

CHAPTER 2

BACKGROUND LITERATURE

2.1 ASSESSMENT AND RANKING OF HAZARD POTENTIAL OF LANDFILL SITES

2.1.1 Introduction

The term 'landfill site' is used in this thesis for any type of site where waste is disposed to land. Landfill sites defined in this manner include a large variety of sites: controlled and uncontrolled, old and new, large and small, operational and non-operational. The potential hazards posed by landfill sites are likely to vary substantially between different sites. An understanding of which site characteristics influence hazards posed by landfill sites forms essential background to the exercise carried out as part of this project classifying landfill sites according to their relative hazard potential (section 3.6.2). The aim of this section (2.1) is to describe factors that influence a landfill site's potential to pose a hazard to the environment and human populations. Also, this section aims to review existing ranking systems developed to classify sites according to the degree of hazard they pose, in order to asses their suitability for use in exposure assessments in epidemiologic studies, particularly the present study.

Firstly, the introduction section will describe definitions of waste used further in this chapters, and introduce the potential pathways of exposure of residential populations to landfill sites.

2.1.1.1 Waste definitions

Different types of landfill sites commonly referred to in the literature and in this thesis are based on broad categories of the waste deposited and can be defined as follows (Department of the Environment, 1995):

- Inert wastes are "wastes that do not undergo any significant physical, chemical or biological transformations".
- Household wastes are wastes arising from private houses and are defined in the U.K. as those wastes arising from domestic properties, caravans, residential homes, nursing homes, and universities, schools and other educational establishments.
- Domestic wastes are synonymous with household wastes.
- Commercial wastes are defined (in the U.K.) as those arising from trade or business, and sport, recreation or entertainment, excluding industrial, and mining and agricultural wastes.
- Municipal wastes are wastes that are "collected and disposed of by or on behalf of the local authority". Municipal wastes generally include household wastes, some commercial wastes, and other local authority wastes i.e. road and pavement sweepings, and construction and demolition wastes.
- Industrial wastes are defined in the U.K. as wastes arising from factories, public transport services, gas, water, and electricity supply services, sewage services, postal or telecommunications services.

The above definitions relate to waste categories as defined by U.K. Department of the Environment. The definition of these broad categories will generally not vary much between countries, although the exact distinction between categories is not always the same. For example, the separation between commercial waste and industrial waste varies between countries, especially where waste from small commercial/industrial enterprises is concerned (Gourlay, 1992).

The definition of hazardous waste is extremely variable. The OECD concluded that although many countries had defined 'hazardous wastes' in their national laws, no two of these are alike (OECD Environment Directorate and UNEP International Register of Potentially Toxic Chemicals, 1988). The approach taken to defining hazardous waste by different countries depends on the purpose and use of the definition (Wilson and Forester, 1987). In many countries the purpose of the definition is to physically separate hazardous from non-hazardous waste, which requires a clear-cut definition. In other countries the definition separates only those wastes for which a specific treatment is required. Many countries specify lists of wastes considered as 'hazardous', defined either by the properties of the waste which render them hazardous (e.g. toxic, corrosive, explosive), by generic waste types/categories (e.g. pesticides, solvents, oily wastes, tars), by industry or technology of origin (e.g. petroleum refining, electroplating), by specific constituents (PCBs, dioxins, lead compounds), or by a combination of some or all of the above (OECD Environment

Directorate and UNEP International Register of Potentially Toxic Chemicals, 1988; Parfitt et al, 1993). The European Communities (EC) directive on Hazardous Waste for example combines lists of generic types of waste, constituents of waste, and properties of waste which render it hazardous (European Communities Council, 1991). The EC definition is fairly recent and many European countries still define hazardous waste according to their existing laws. U.K. law for example includes definitions of 'controlled waste', 'special waste', 'difficult waste', and 'clinical waste', which may all include hazardous wastes as defined by the EC Directive.

Theoretically, any waste has the potential to be hazardous if not handled in a satisfactory manner (House of Lords Select Committee on Science and Technology, 1989), so wastes and waste sites classified as non-hazardous by any definition cannot automatically be discarded in the evaluation of health risks.

Different types of landfill sites are often referred to using the broad categories of waste, as described above, that were deposited at the site. So a site can be a 'municipal' waste site or an 'industrial' waste site. Landfill sites often, especially in the past, took wastes from different categories, mixing household waste with industrial waste for example. The official practice of 'co-disposal' used to be common in many countries, and still is in some, particularly the U.K. Co-disposal is "the disposal, in landfills, of a restricted range of industrial wastes (including some hazardous wastes), together with decomposing municipal waste or similar degradable waste, in such a way that the industrial waste gradually undergoes a form of treatment" (Westlake, 1995). Although some research has shown that co-disposal can be effective in reducing the hazard related to the disposal of certain groups of chemicals (Knox, 1990), the practice of co-disposal has also been criticised for posing a greater hazard than mono-disposal sites in case some of the hazardous wastes do not undergo treatment within the site. This may happen for example when the ratio of disposed hazardous wastes to other wastes is too large (Westlake, 1995). Concerns exist about the lack of evidence that the co-disposal theory of treatment of hazardous waste within other waste, works well in practice (Westlake, 1995). Co-disposal is banned in the U.S., and a ban has been proposed for new European sites through the draft EC Landfill Directive (European Communities Council, 1991).

The following sections consider landfill sites in general, not any specific type of landfill or any specific type of waste. Differences between types of landfills and wastes deposited which may influence the hazard potential of a site will be pointed out.

2.1.1.2 Potential routes of exposure

Two major processes within a landfill govern the migration of chemicals into the surrounding environment: leachate production and landfill gas generation.

Leachate is the liquid generated within a landfill as the result of compression and degradation of wastes, and percolation of water (rain, surface, or ground water) through the waste (El-Fadel et al, 1997; Lisk, 1991). Landfill leachate contains the soluble components of the waste, both organic and inorganic. Leachates containing contaminants from landfill sites can form an important threat to groundwater and surface water near the site(Campbell, 1993). The composition of leachate and evidence for migration of leachate into the environment surrounding landfills is discussed in section 2.2.1.

Landfill gas is also produced during degradation of the waste in a landfill and consists predominantly of methane and carbon dioxide (El-Fadel et al, 1997; Lisk, 1991). Landfill gas will be produced in any site containing biodegradable waste. Landfill gas poses an explosion hazard due to the large concentrations of methane present. Numerous volatile organic chemicals (VOCs) may be emitted into the air with the landfill gas in small concentrations, usually less than 1% of the gas emissions (El-Fadel et al, 1997; Lisk, 1991; Office of Technology Assessment, 1989). These so-called trace gases can be formed both indirectly, during the biological degradation of complex organic compounds, and directly from volatilisation of organic compounds present in the deposited waste (Campbell, 1993). In order to be emitted into the air, trace gases within buried waste must be transported upwards through the waste. The generation of landfill gas in sites containing biodegradable waste accelerates this transport (Grisham, 1986; Lewis-Michl et al, 1998).

Evidence for off-site migration of toxic chemicals via landfill gas and other routes is discussed in section 2.2.1.

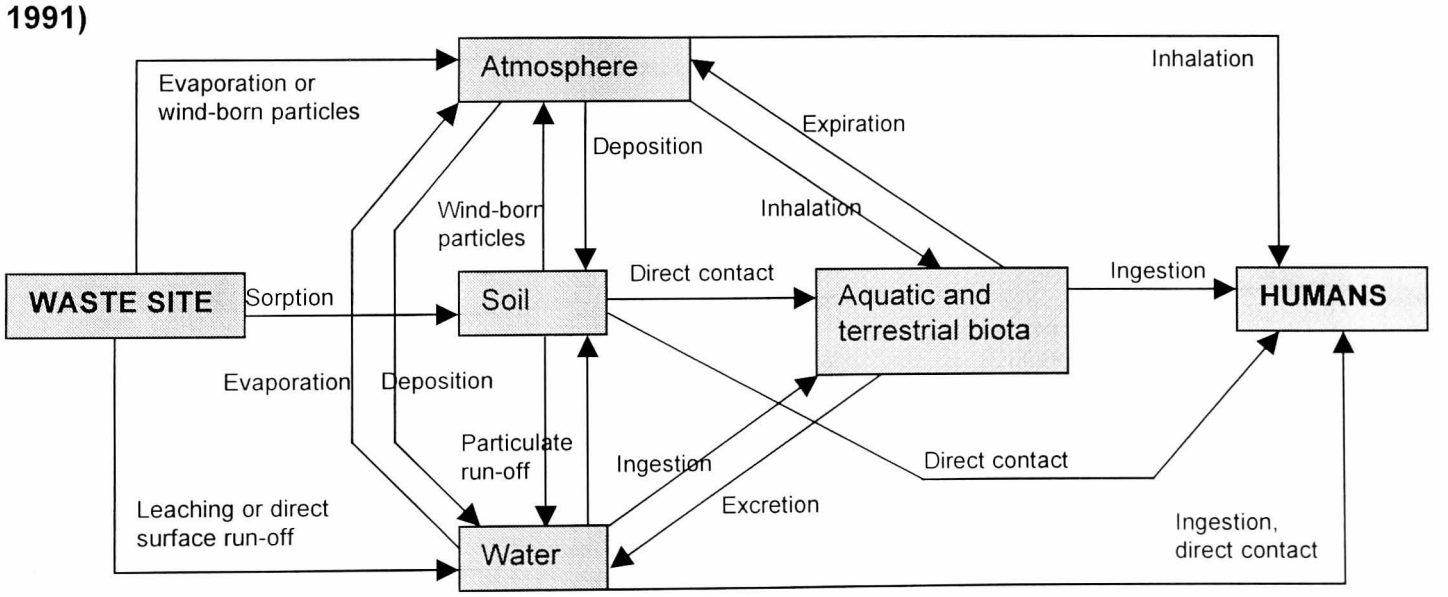
Leachate and landfill gas generation are usually considered the most important sources of environmental problems associated with landfill sites (Westlake, 1995). In addition, landfill sites may be the source of pollution via other processes, including (Campbell, 1993; Eduljee, 1998; Westlake, 1995):

- run-off of contaminated water from the surface of the landfill;
- emission of volatile chemicals into the air independently from landfill gas emissions as a results of direct volatilisation during waste deposition and from on-site leachate pools (Eduljee, 1992; James and Stack, 1997);
- dust emissions, including dust and particle-bound chemicals, during the dumping of waste or through wind erosion;
- wind-blown litter from the site;

- emissions from inefficient gas flares;
- spills from the vehicles transporting waste to and from the site;
- problems related to birds, vermin, and insects at a site, including the potential for spread of disease;
- and noise and odour pollution.

The potential pathways of transport of contaminants released through landfill leachate, gas, or other processes from a site to human populations are shown in Figure 2.1. Possible exposure media include water, air, food and soil (National Research Council, 1991; Upton, 1989). When a site is located near an aquifer used for drinking water extraction this may cause exposure of the population serviced by this aquifer, although not necessarily of residents nearby the site. Nearby residents may be exposed, if their water is extracted from local wells, through consumption of the water and/or through direct contact and inhalation during bathing and washing. In many situations drinking water supply of residents does not originate from the local area. For people living in the vicinity of these sites, other routes of exposures may be of more concern: airborne toxic chemical contamination via landfill gas and particles and chemicals adhered to dust; direct contact with contaminated soil and/or surface water; pollution of indoor air in the case of evaporation of volatile organic chemicals from groundwater or soil gas into basements of nearby houses; and contamination via the food chain in case of consumption of home-grown vegetables or locally caught fish.

Figure 2.1: Potential pathways of exposure to landfill sites (National Research Council, 1991)



Potential exposures via the pathways described above will generally be of a chronic nature apart from in accidents such as fires and major spillages. Most of the pathways will play a role both during operation of a site and after site closure, with the exception of pathways

associated directly with site operation such as the generation of dust during waste dumping and spills from vehicles transporting waste.

Evidence of off-site contamination and exposure of humans occurring via the possible pathways described here, is evaluated in section 2.2.

2.1.2 Site characteristics affecting hazard potential

Site specific conditions that may influence a landfill site's potential to cause exposure to nearby residential populations can be divided into (Table 2.1):

- factors that influence the generation and composition of leachate and landfill gas,
- factors that influence the ease with which contaminants may migrate off-site (beyond the site boundaries) and contaminate the surrounding environment,
- factors that influence whether the residential population will come into contact with contamination.

Table 2.1: Factors affecting hazard potential of landfill sites

1) Factors affecting generation and composition of leachate and landfill gas
   - waste type
     - amount of biodegradable wastes
     - types of chemicals deposited
     - properties of individual chemicals present: i.e. solubility, volatility
     - interactions (chemical, physical) between chemicals
   - age of waste
   - quantity of waste
   - waste density
   - depth of waste
   - pH, moisture content, and temperature within waste

2) Factors affecting off-site migration of leachate, and gas and particulate emissions
   - design and management
     - 'dilute and disperse' or 'containment' principle
     - lining
     - leachate collection
     - covering and capping
     - gas collection
     - monitoring
   - geology and hydro-geology
     - soil type, permeability
     - depth to groundwater
   - topography
     - steep hills, flat lands, floodplain
   - climate
     - rainfall
     - wind force and direction

3) Factors affecting contact of nearby residential population with off-site contamination
   - land use
     - recreation
     - local food growing: allotments
   - surface water use
   - presence of drinking water wells for local use

2.1.2.1 Factors affecting generation and composition of leachate and landfill gas

Waste degradation, and thereby the generation, composition, and toxicity of leachate and landfill gas, is governed by complex physical, biological and chemical processes. Some of the basic factors that influence these processes are known but, as Robinson and Gronow (1992) point out, an understanding of all parameters and steps "is almost completely lacking" and therefore predictions of leachate and gas composition at specific landfill sites are currently impossible to make. This section describes some of the basic factors that are known to affect gas and leachate production and composition.

Firstly, the amount of biodegradable, organic, wastes determines the amount of both leachate and landfill gas in a landfill. A site which contains totally inert waste will not generate landfill gas. The rate of biodegradation in a landfill also depends on factors such as the density, depth, quantity, pH, moisture content, and temperature of the waste (Westlake, 1995). Rainfall is the main contributor to the water content of a site and therefore importantly influences the amount of leachate that is generated (Lema et al, 1988).

The composition of landfill gas and leachate is determined by the types of chemicals deposited, properties of the individual chemicals, such as their solubility and volatility, and interactions between chemicals. The composition of gas and leachate may bear little resemblance to the composition of the wastes deposited because of the biological, chemical, and physical reactions that take place within a site.

Hazardous wastes are generally assumed to give rise to more toxic leachates and gases than 'non-hazardous' wastes because larger concentrations of toxic chemicals are present in such wastes (Office of Technology Assessment, 1989). Landfill gas for example, has been reported to contain a wider range of toxic chemicals at sites where industrial wastes were deposited compared to those containing only municipal waste (Young and Parker, 1983). Pavelka et al (1993) report higher concentrations of selected toxic substances in leachates from sites containing only hazardous waste than from co-disposal sites (municipal, industrial, and hazardous waste). The opposite has also been reported: leachates from domestic wastes and co-diposal wastes were significantly more toxic than those from purely industrial hazardous waste in a French study testing the toxicity of 27 landfill leachates (Bernard et al, 1996). A report with preliminary findings from the California Landfill Testing Program which includes sampling data from 340 sites, concludes that hazardous and non-hazardous waste sites appeared similar in their ability to produce toxic gases (Baker et al, 1990). Several authors have concluded that toxic compounds can be found even in leachates and landfill gas from reportedly purely municipal waste sites and

that municipal sites must for that reason be considered just as potentially hazardous as industrial sites (Bernard et al, 1996; Brown and Donnelly, 1988; El-Fadel et al, 1997; Westlake, 1995). This is thought to be due to toxic compounds present in regular household from for example pesticide, paint and battery wastes, to unrecorded and/or illegal disposal of industrial wastes in municipal sites, and to the transformation of non-hazardous substances during waste degradation processes (El-Fadel et al, 1997; Reinhart, 1993).

Physical and chemical characteristics of chemicals importantly determine their movement and fate in environmental media: water, soil, and air (Andelman, 1987). More soluble chemicals will tend to be transported more easily in leachate and groundwater, volatile chemicals will tend to be emitted into the air. The chemical reactivity of a substance determines how resistant it is to undergoing degradation reactions that change its chemical state. For example, halogenated organic compounds are more stable, less likely to degrade, the higher the number of halogen atoms: carbon tetrachloride for example, is more stable than methyl chloride (Andelman, 1987).

The age of the waste in a site affects the rate of decomposition of the waste and thereby the quantity and composition of leachate and landfill gas generated (Lisk, 1991; Westlake, 1995). Lisk (1991) reports that concentrations of most compounds in leachate, including heavy metals, decrease with the age of the waste. Similarly, several authors have pointed out that concentrations of volatile organic compounds (VOCs) in landfill gas tend to be highest in early stages of waste decomposition (Campbell, 1993; Ward et al, 1996). However, it has also been documented that a 20 year old municipal waste site still produced landfill gas with significant concentrations of VOCs, including vinyl chloride (Allen et al, 1997).

2.1.2.2 Factors affecting off-site migration of contaminants

Proper design and management of a landfill is important in order to minimise the potential for leachate, landfill gas, and other emissions to migrate off-site and pollute nearby water, soil, and air. The principles and regulations of landfill design and management have changed substantially over the last two decades in Europe with increasing emphasis on the protection of the surrounding environment (Westlake, 1995). The following design and management factors are important in assessing a site's hazard:

- Design of the site. Landfill designs follow two basic principles: 'dilute and disperse' (or 'dilute and attenuate') and 'containment'. Dilute and disperse sites do not try and prevent migration of leachate into the surrounding environment but rely on attenuation (through adsorption, biodegradation, chemical reactions, dilution, and filtration) of contaminants in the surrounding soil and dilution within the groundwater to such degree that concentrations of contaminants do not pose a risk (Office of Technology Assessment, 1989; Westlake, 1995). These sites have little or no engineering of their base or sides. In the U.K. this principle was applied to the majority of landfill sites until the end of the 70s. The effectiveness of dilute and disperse sites in preventing groundwater pollution has been seriously questioned (Office of Technology Assessment, 1989). New sites in both the U.K. and elsewhere in Europe are now required to use the containment principle which does not allow migration of leachate off-site. In practice however, a containment site is defined as one "where the rate of release of leachate into the environment is extremely low" (Westlake, 1995) and much of the debate currently focuses on what rate of release is acceptable. Complete containment for an indefinite time would be very hard to achieve, and all landfills must be expected to cause some degree of release of leachate into the environment at some point in time (Campbell, 1993; Westlake, 1995). It has been pointed out that the first 2 to 3 decades of a containment site may pose relatively little threat to groundwater but over longer time periods this cannot be guaranteed (Mather, 1989).

- Lining. In containment sites the sides and base of the site are lined, which means that they are engineered with a natural and/or synthetic material to prevent leachate from migrating beyond the site boundaries. The materials used to construct the liner determine it's permeability, durability, and resistance to chemical breakdown (Westlake, 1995). The long-term resistance of liners is not always known and punctures and cracks in liners can cause serious problems (Campbell, 1993).

- Leachate collection. Leachate collection systems are increasingly being installed to remove leachate from the base of a containment landfill, above the lining, to prevent the leachate accumulating in the waste. After collection the leachate can be discharged to a sewer, be recirculated through the landfill, or undergo biological or chemical treatment at the site (Westlake, 1995). It has been pointed out that a leachate removal and/or treatment system is essential for the effective management of environmental risks associated with leachate (Westlake, 1995). A study in Ireland however found increased levels of VOCs in ambient air at one part of a landfill site where a leachate collection system had been installed compared to a part that had no leachate collection: the

leachate was collected in a pool at the site and left open to the atmosphere before undergoing biological treatment (James and Stack, 1997).

- Covering and capping. During the period of active operation of a site wastes should be covered daily to prevent emissions of dust, particles, and windblown litter. This cover commonly consists of a thin layer of soil or rubble. After closure of the site or part of the site a cap can be applied to the site in order to prevent water, mainly from rainfall, from entering the site, thereby reducing leachate generation (Office of Technology Assessment, 1989). Landfills with no or incomplete capping have been found to produce more leachate than those with complete capping (Pavelka et al, 1993). The presence and type of covering and capping will also affect the pathway of migration of landfill gas: gas will follow the path of least resistance and where only a daily, gas-permeable, cover is present gas will tend to vent through this surface (Westlake, 1995). The presence of a sealed cap will prevent this and gas will tend to migrate laterally, depending on the lining of the site and the geology around the site. The rate of vaporisation of VOCs has been reported to depend amongst other factors, on the type of cover used (Bennett, 1987).

- Gas collection. Gas migration can not easily be prevented and measures such as capping and lining will merely influence the pathway of gas migration (Westlake, 1995). A system to abstract gas from within the landfill should therefore be incorporated in the design of any landfill that is expected to generate gas. Gas abstraction systems can be passive or active. In passive systems gas is collected through wells or trenches and vented directly into the atmosphere. Although such systems prevent lateral migration of landfill gas they generally increase emissions, including trace gases, from the surface of the landfill (Westlake, 1995). The U.K. Department of Health states that passive venting systems should only be used at sites with a low rate of gas generation (Department of the Environment, 1995). Other systems actively abstract gas after which it can be flared off or used in energy recovery systems. Flaring does not remove all trace gases but reduces concentration before emitting to the atmosphere (Eduljee, 1998; Westlake, 1995). The possibility that some toxic chemicals, including dioxins and furans, may actually be formed by the flaring has been discussed (Brosseau and Heitz, 1994; Cram and Parkinson, 1992).

- Monitoring. Proper management of both leachate and landfill gas should include regular monitoring (Campbell, 1993). For leachate this should include monitoring of the levels within the site, amount and composition migrating off-site, and ground and surface water nearby the site. Gas is usually monitored for the amount of methane produced, not for

trace emissions of volatile organic compounds. Campbell (1993) notes that in some countries (U.S., Germany) levels of VOCs in gas emissions from landfill surfaces are restricted. In California all active and some inactive landfills are by law required to be monitored for toxic components in landfill gas, in air above the landfill surface and beyond the site boundary, and in underground gas migration (Baker et al, 1990). In the U.K. monitoring guidelines recommend monitoring for the major landfill gases (methane, carbon dioxide and oxygen), not for trace gases (Department of the Environment, 1994).

In addition to the design and management of a site, its local geology and hydrogeology play a role in determining off-site migration of contaminants. For example, the permeability of the soil surrounding the landfill will determine the ease with which leachate may filter through the soil and reach the groundwater level. Sandy soils are the most permeable whereas clay soils provide least permeability unless cracks are present in the clay. Sandy soils also provide little organic sorption which means that organic contaminants can filter through the soil without undergoing transformation (Barker et al, 1986). Local hydrogeology determines the movement of pollutants in groundwater (Lisk, 1991). The depth of the groundwater from the landfill base also influences the ease with which contaminants can reach groundwater.

A site's topography may be important also. For example, sites on steep hills may encounter problems with erosion and surface water run-off, and floodplains are usually considered unsuitable for landfills (Brown et al, 1983).

Climatic conditions can influence off-site migration of contaminants in various ways: through winds affecting transport of gas and particulates, rainfall affecting the moisture content of the waste therefore leachate production, and temperature affecting biodegradation, volatility of chemicals, and run-off potential (Brown et al, 1983).

2.1.2.3 Factors affecting contact of nearby residential populations with off-site contamination

In addition to conditions at the landfill site, factors in the environment surrounding the landfill will determine whether or not residents near the site may come into contact with contamination from the site. Such factors include land use for recreation (playing fields, parks, sports fields), food growing for local consumption (allotments), use of surface water for swimming and/or fishing, and the presence of drinking water wells for local use.

2.1.3 Hazard potential ranking systems

A number of methodologies have been developed to score and rank the hazard potential of hazardous waste sites taking account of the site characteristics discussed in the previous sections. Reasons for the development of such methodologies have been three-fold: for the identification of sites that are priorities for clean-up (JRB Associates, 1982; United States Environmental Protection Agency, 1990), for public health assessments (Allred et al, 1993; New York State Department of Health, 1986), and for exposure classification in epidemiological studies on health effects of waste sites (Croen and Shaw, 1996; Marshall et al, 1993). The vast majority of the work on hazard ranking of landfill sites has been carried out in the U.S. The development of a U.K. scoring system for use in landfill site inspections, HALO (Dames&Moore International, 1988), was abandoned because the questionnaires to collect necessary data were considered too long and complicated. The HALO system required information from landfill operators, site inspectors and the water authority on over one hundred factors.

In 1982 the U.S. Environmental Protection Agency (U.S.EPA) developed the Hazard Ranking System (HRS) to determine which sites to include on its National Priorities List: a list of sites that have priority for further investigation and, if necessary, remediation, under the Superfund clean-up programme (United States Environmental Protection Agency, 1990). In the 1990 HRS four pathways (groundwater migration, surface water migration, soil exposure, air migration) are scored in 3 categories: likelihood of release, characteristics of the waste, and people or sensitive environments affected by the release. The final score is calculated using both addition and multiplication of composite factors. For each pathway likelihood of release is scored using information on observed releases if possible. Where such information is not available 'potential to release' is scored on the basis of factors such as containment, lining, capping, leachate and gas collection and depth to groundwater. The waste characteristics component requires information about the types of chemicals present, their concentrations, and their most likely pathway. The HRS uses information from existing site documentation and from site inspections in which environmental and waste samples are collected to determine what substances are present in a site. The HRS has been criticised for not taking sufficient account of all possible human exposure pathways (New York State Department of Health, 1986), and for not being able to adequately define and control the influence of individual factors in the system (Haness and Warwick, 1991). Haness and Warwick (1991) found the influence of certain factors on the final score to depend on the scoring of other, unrelated, variables because of the way factors were multiplied and added

up. This illustrates the difficulties involved in capturing complex relationships between many site characteristics within a systematic scoring system.

The HRS was not developed to specifically assess public health hazards from waste sites. Therefore, the Agency for Toxic Substances and Disease Registry in the U.S. developed a separate Site-Ranking System (SRS) with as aim to identify sites that pose the greatest hazard to public health after they had been listed as NPL sites (Allred et al, 1993). This system requires limited environmental sampling data and includes information about community health concerns and health outcomes. Health outcome data are collected from routine statistics, hospital discharge records, community health surveys, and/or epidemiological studies.

The New York State Department of Health (New York State Department of Health, 1986) developed a system based on the HRS, which requires similarly detailed data input, but uses a different structure of multiplication and addition of factors. This system claims to evaluate possible human exposure pathways in more detail. For example, it includes exposure to vapours in basements, dermal contact with contaminated soil, and use of surface water for fishing. Both Geschwind et al (1992) and Marshall et al (1993) based residential exposure classifications in epidemiological investigations on this system. Marshall found that for most sites little sampling data were available to evaluate actual off-site exposure, and on-site concentrations had to be extrapolated to off-site ones.

Croen and Shaw (1996), in an epidemiological study of residence near waste sites and risk of bith defects, classified National Priority List sites in California according to exposure potential (definite, potential, no exposure) in each of 5 pathways. An industrial hygienist followed a decision tree for each pathway to come to the final exposure classifications. As a validation exercise 10% of sites were evaluated by another person. Discrepancies were few and did not influence the final classification of sites. Again detailed information on chemicals of concern and concentrations on and off-site from environmental sampling was needed to apply the classification system. In this study non-NPL sites could not be classified since only limited information on these sites was available.

In the early 1980s JRB Associates developed for the U.S.EPA a system to identify landfill sites for clean-up priority that did not require extensive site investigations and was aimed for use with readily available information (JRB Associates, 1982). The authors stated that the "validity of the system was tested at sites across the country" and that "New Jersey officials agreed that ratings of 30 sits in their State were good reflections of the true hazard potential of the site". Results of such validation exercises are not included in the report however.

A general problem with ranking systems is that where more data are available, scores tend to be higher, even though sites with little data, for example because of poor record keeping, may be the more hazardous ones. For example, Haness and Warwick (1991) in their evaluation of the U.S.EPA Hazard Ranking System found that by adding previously missing information on the factor 'hazardous waste quantity' to a large number of possible site scenarios, scores increased and up to 46% of the sites crossed the cut-off for inclusion on the NPL list. Also, where less information is available scoring is based more on assumptions and less on actual measurements. There is little information in the literature about the validity of the scoring systems presented here. For example, rankings have generally not been compared to actual exposure measurements in residential settings. The absence of information on the validity of these ranking systems makes it difficult to assess the extent to which misclassification of sites may occur in the hazard rankings.

In conclusion, although it is possible to indicate which factors may influence the likelihood that a landfill site causes contamination of surrounding areas (section 2.1.2), a full understanding of the relative importance of the different factors and of interactions between factors, seems to be lacking. It is therefore very difficult to integrate the many factors that may play a role into one systematic ranking system. Most existing systems are complex and require very extensive information on characteristics of sites, much of which may only be obtainable through site investigations including on and off-site sampling. Also, most existing systems require detailed information on the types of waste deposited at a site. Resources of epidemiological studies are generally not sufficient to undertake site investigations. Epidemiological studies in the U.S. have benefited from the availability of site information collected under the Superfund programme (Croen and Shaw, 1996; Geschwind et al, 1992; Marshall et al, 1993) (section 2.4).

2.2 EVIDENCE FOR HUMAN EXPOSURE

An important question in assessing health risks from waste landfill sites is whether chemicals present in sites cause exposure of nearby residents, and if so, via which pathways and in what dose. This section reviews existing evidence for migration of chemicals from landfill sites into the surrounding environment and for human exposure resulting from such off-site contamination.

Firstly, section 2.2.1 evaluates evidence from environmental monitoring and sampling data for migration of chemicals from landfill sites into the surrounding environment where exposure of nearby residents may occur. Secondly, section 2.2.2 presents evidence for actual exposure from personal and biological monitoring of human populations: landfill workers and residents.

2.2.1 Off-site migration of contaminants

Literature on the monitoring of substances from landfill sites in the environment surrounding landfill sites can broadly be divided into two main pathways: leachate affecting groundwater, surface water and drinking water, and landfill gas, dust and particulate emissions affecting air quality. This section describes published literature on off-site migration of chemicals via these two pathways and attempts to answer the following questions: which chemicals may be of concern? in what concentrations may they be present in the environment surrounding a landfill? and up to what distance from a landfill may they be detectable?

2.2.1.1 Water pathway

Leachate

Leachate from landfill sites may contaminate surrounding soil, groundwater, surface water, and ultimately drinking water as was described in section 2.1. Leachate contains mainly organic degradation products, but may, depending on waste composition and processes within the waste site, include relatively low concentrations of organic and inorganic toxic chemicals (Christensen, 1992). Numerous studies on the composition of leachates from municipal, hazardous, and co-disposal sites have detected a wide range of substances including aromatic and halogenated hydrocarbons, heavy metals, pesticides, phthalates, and

some dioxins and furans (El-Fadel et al, 1997, Christensen, 1992 #1376; Lisk, 1991; Pavelka et al, 1993; Reinhart, 1993; Robinson, 1995; Schultz and Kjeldsen, 1986). Leachate quality data is generally based on single samples at a particular stage of a particular landfill (Robinson and Gronow, 1992), and from this data it is not possible to predict the 'typical' composition of landfill leachate. The Department of the Environment reports typical household waste leachate compositions in Waste Management Paper 26 which indicate that heavy metals are present in low concentrations in such leachates: lead 0.05-0.60 mg/l, cadmium 0.005-0.01 mg/l, chromium 1 mg/l (Robinson, 1995). Concentration ranges for other toxic chemicals are not given.

Groundwater

Releases of leachate to groundwater have been documented by numerous studies as reviewed by Lisk (1991) and El-Fadel et al (1997). Groundwater was the environmental medium most often related to observed releases of contaminants at U.S. National Priority List municipal landfills (Office of Technology Assessment, 1989). 132 out of 163 municipal NPL sites (72%) were associated with groundwater releases. The 15 most frequently detected organic compounds in groundwater at waste sites in Germany and the U.S. include mainly aliphatic chlorinated hydrocarbons (tetrachloroethylene, trichloroethylene, vinyl chloride, dichloroethylene, dichloromethane, trichloromethane, trichloroethane) and aromatic hydrocarbons (benzene, toluene, ethyl benzene) (Christensen, 1992). The main substances for which migration into groundwater had been documented at 951 National Priority List sites in the U.S. were heavy metals (lead, chromium, arsenic, cadmium, mercury) and volatile organic compounds (aliphatic chlorinated and aromatic hydrocarbons), both documented at around 25% of sites (National Research Council, 1991). PCBs, PAHs, phthalates, pesticides, and dioxins had also been documented in groundwater, but at far fewer sites (<5%). A study of groundwater pollution at 16 Finnish waste sites found heavy metals more frequently present in significant concentrations than organic chemicals (Assmuth and Strandberg, 1993). This study reported concentrations of several toxic leachate components (arsenic, lead, dichloromethane, 1,2 dichloroethane) in groundwater within 200 metres of waste sites to be above groundwater quality guidelines.

Although information is available on the frequency with which specific chemicals have been detected in groundwater at landfill sites or in their immediate vicinity, information on the on the transport and possible attenuation of specific toxic chemicals in groundwater pollution plumes from landfills is largely lacking. Leachate pollution plumes are usually mapped using chloride as an indicator because chloride is relatively unaffected by reactions such as

degradation and adsorption (Lisk, 1991). Such reactions are likely however to affect other contaminants that may be present in the leachate. Heavy metals for example, although commonly present in leachate, do not often pose a groundwater pollution problem because they undergo strong attenuation by sorption and precipitation in the plume and will not be transported far with the plume (Christensen, 1992). Other compounds, for example benzene and some pesticides, may be relatively persistent in the plume (Christensen, 1992). Barker et al (1986) found aromatic hydrocarbons (mainly substituted benzene) to spread untransformed through the groundwater plume of a municipal landfill to distance of up to 700 m, whereas biotransformation restricted chlorinated hydrocarbons (1,1,1-trichloroethane and trichloroethylene) to the immediate vicinity of the waste site. Christenen (1992) in a review of attenuation factors leachate transport concludes that the prediction of transport of leachate pollutants other than chloride in groundwater is currently not possible since very few studies have mapped the transport of specific pollutants from landfills. Pollution plumes in groundwater, measured by chloride, have been documented to extend for hundreds of metres outside landfill sites: 400m (Christensen, 1992), 700m (Barker et al, 1986; MacFarlane et al, 1983) and even up to 3,000 metres (Christensen, 1992). Lisk (1991) in a review of environmental effects of landfills states that "movement of contaminants in groundwater can extend distances of up to a kilometre or more". Others have found leachate pollution to be restricted the immediate vicinity of sites (Baxter, 1985; Rugge et al, 1995).

Drinking water

For residents near waste sites groundwater pollution would be of most concern if local wells for extraction of water for drinking or other domestic uses were affected by such pollution. Such incidents have been documented in the U.S. (Lagakos et al, 1986; Wrensch et al, 1990; Harris et al, 1984). Chemicals of main concern in these drinking water pollution incidents have been chlorinated organic compounds. A pesticide dump in Hardeman County, Tennessee (Clark et al, 1982; Harris et al, 1984), caused pollution of local wells with carbon tetrachloride in concentrations exceeding the WHO drinking water guidelines more than 10,000 fold. High concentrations of chloroform, tetrachloroethylene, benzene and chlorobenzene were also found. In Santa Clara County, California, an underground storage tank polluted a groundwater derived drinking water supply with organic solvents, mainly 1,1,1-trichloroethane (methyl chloroform). Trichloroethane concentrations exceeded the State's action level 8.5 times (Wrensch et al, 1990). In Woburn, Massachusetts, waste dumps had caused the contamination of municipal wells via groundwater and again organic solvents, including trichloroethylene, tetrachloroethylene, chloroform, and dichloroethylene, were found to be the main pollutants of concern (Lagakos et al, 1986). Trichloroethylene was

found in concentrations exceeding WHO guidelines (World Health Organization, 1993). Studies of health effects in relation to the drinking water pollution incidents reported here are discussed in section 2.4.3.4.

Surface water

Little information is available from published literature about pollution of surface water by contaminants from landfill sites. The National Research Council (National Research Council, 1991) reports that migration of heavy metals into surface water was documented at 138 out of 951 National Priority List (NPL) sites (15%), migration of volatile organic compounds at 88 sites (9%), and migration of PCBs, PAHs, phthalates, pesticides, or dioxins at under 5% of sites. The OTA reports observed releases of substances to surface water at around 45% of municipal landfill sites (Office of Technology Assessment, 1989). The OTA concludes that it is not possible to determine the overall extent of surface water contamination by municipal landfills in the U.S. because the general lack of monitoring.

2.2.1.2 Air pathway

Landfill gas

Landfill gas trace components have been reported to include a wide range of potentially toxic and odourous compounds, including aromatic hydrocarbons (benzene, toluene), halogenated hydrocarbons (trichloroethylene, tetrachloroethylene, vinyl chloride, chloroform), and organosulphur compounds (hydrogen sulphide) (Gendebien et al, 1992). Commonly, around one hundred different trace VOCs are detected in landfill gas from municipal and co-disposal waste sites (Allen et al, 1997; Scott et al, 1988; Young and Heasman, 1985). The range of compounds detected in landfill gas from different sites and in different studies is very similar but concentrations of individual trace compounds vary widely.

Several studies have reported concentrations of volatile organic compounds in pure landfill gas as extracted directly from within the site, and compared such concentrations with occupational exposure limits based on 8-hour weighted average levels (Allen et al, 1997; Harkov et al, 1985; Ward et al, 1996; Young and Parker, 1983), or background environmental levels (Assmuth and Kalevi, 1992). Results of these studies are summarised in Table 2.2. In most studies only a limited number of compounds was found to exceed comparison limits.

Table 2.2: Trace volatile organic compounds detected in landfill gas

Reference	*Sites studied*	*Number of trace compounds detected*	*Comparison values used*	*Compounds found in excess of comparison value*
Measurements in 'pure', undiluted landfill gas, before emissions into ambient air				
Young and Parker, 1983	6 UK landfill sites : 3 domestic waste only, 2 domestic/industrial waste, 1 industrial waste	over 30 aromatic and halogenated trace organic compounds	NIOSH time-weighted average threshold limit value (TLV)	benzene (4 sites), metahethiol (2 sites), butaethiol (1 site), methanol (1 site), toluene (1), xylene (1), propyl benzene (1), tetrachloroethylene (1), vinyl chloride (: sites)
Harkov et al, 1985	6 abandoned hazardous waste sites, 1 municipal waste site, in New Jersey	results for 23 volatile organic compounds reported	background urban levels in New Jersey	8 out of 23 VOCs generally exceed urban background levels. Not specified which compounds.
Scott et al, 1988	3 UK municipal waste sites	136 compounds of which 109 at each site	8 hour weighted average toxicity threshold limit values (TLV)	benzenes, ethanol, propan-1-ol, butan-2-ol, dichloromethane, dichlorofluoromethane, carbon disulphide, methanethiol, hydrogen sulphide, formaldehyde
Assmuth and Kalevi 1992	3 old and 1 active municipal waste landfill sites (with co-disposal of industrial waste) in Finland	not reported	background urban air levels; lowest of Finnish or US occupational standard	many compounds, including benzene, toluene, trichloroethylene, tetrachloroethylene above urban air quality limits. Only few exceeded occupational limits: chloroform, carbon tetrachloride, benzene
Westlake 1995 (from Clay and Norman, 1988)	landfill gas from UK sites (not known how many sites)	not reported	UK occupational exposure level (OEL)	benzene, toulene, xylene, propyl benzenes, dichloroforomethane, vinyl chloride, 1,2-dichloroethylene, tetrachloroethylene
Ward et al, 1996	1 UK landfill site: municipal and industrial waste	79 volatile organic compounds	UK HES long-term exposure limit (LTEL, also MEL)	outside site boundary in soil: vinyl chloride (40m distance from site), dichlorofluoromethane
Allen et al, 1997	7 UK municipal landfill sites	140 compounds of which 90 at each site	UK 8 hour weighted average occupational exposure standard (OES), or maximum exposure level (MEL)	MEL: vinyl chloride (2 sites); OES: toluene (1 site), xylene (1 site), trimethyl benzenes (1 site), tetrachloromethane (1 site), dichlorofluoromethane (3 sites)
Measurements in ambient air above landfill surface				
Bridges et al, 1996	1 UK landfil site, mainly municipal, some industrial waste	14 VOCs measured: 2, 5, and 10m above surface	UK OES	all 14 compounds at least 1,000 fold under occupational limits
James and Stack, 1997	municipal and non-hazardous industrial waste site in Ireland	11 VOCs measured: 2 m above surface	WHO air quality standards	benzene exceeded WHO ambient air limit. Benzene, toluene, ethylbenzene, xylene 5-13 times higher than typical UK rural concentrations and similar to urban concentrations. Other compounds no comparison values available.

Compounds found to exceed exposure limits in more than one study include suspected carcinogens vinyl chloride and benzene. The different exposure limits used vary considerably, for some compounds up to a factor 10. For example the TLV for benzene used by Young and Parker (1983) is 3.25 mg/m^3 and the OEL for benzene used by Westlake (1995) is 30 mg/m^3. Further, it should be noted that the exposure limits used do not take account of exposure to a chemical mixture such as landfill gas and assume synergistic and additive effects not to occur within these mixtures (Allen et al, 1997). Very little data exists on the potential for such effects.

Ambient air at waste sites

The above studies measure concentrations of toxic components in landfill gas within sites, before emission to the ambient air. However, whether concentrations of these compounds are still high enough to represent a health risk after release into the air, either to site workers or to nearby populations, largely depends on the degree of dilution of the landfill gas as it leaves the landfill surface (Allen et al, 1997; Young and Parker, 1983). Young and Parker (Young and Parker, 1983) in an assessment of landfill gas hazards at 6 U.K. sites report that in general a 100-fold dilution in the air should ensure toxic components in landfill gas to reach concentrations where they do not represent a risk to health at long term exposures. Such dilutions should be easy to achieve. It has for example been reported that methane (the main component of landfill gas) is typically diluted over one thousand-fold within the first two metres above the landfill surface (Young and Heasman, 1985). Bridges et al (1996) carried out an exposure study of workers at a U.K. landfill and measured 14 VOCs in the ambient air at 2, 5, and 10 metres above the surface of the landfill. Concentrations of these VOCs were all more than 1,000 fold lower than U.K. occupational exposure limits. The 14 VOCs did not include compounds found to exceed limits in other studies, apart from dichlorofluoromethane. Benzene and vinyl chloride were not analysed for example. James and Stack (1997) measured VOCs 2 m above the landfill surface of an Irish site. Benzene was the only compound out of 11 VOCs analysed found to exceed WHO ambient air quality standards (by a factor 5), other compounds were found in concentrations similar to typical urban air values.

Ambient air at residential locations

There are few published studies giving measured concentrations of trace gas components in ambient air at distances away from landfill site boundaries where residential populations would be exposed to the chemicals. Table 2.3 shows concentrations of volatile organic compounds measured in ambient air near landfill sites. Not all compounds measured in the

respective studies are shown, only those that were common to two or more studies. The measurements given in Table 2.3 are based on one-off investigations of individual sites, with the exception of the Californian study which is based on nearly 300 landfills. Differences between studies in sampling locations relative to the landfill site and in meteorological conditions make comparisons between studies extremely difficult.

At the French industrial and household waste site of Montchanin, one of the sites included in the EUROHAZCON study, odour complaints from residents led to measurement of VOCs in ambient air both at the site and several off-site locations (Deloraine et al, 1995; Zmirou et al, 1994). The total concentration of VOCs decreased from 1364 $\mu g/m^3$ at the site 1.5 m above the surface, to 433$\mu g/m^3$ 100 metres downwind from the site at the nearest house, and 192$\mu g/m^3$ in the town centre 600-700 m from the site (Table 2.3). Concentrations of aromatic, halogenated, and other hydrocarbons, decreased greatly also with distance from the site. The Belgium site of Mellery has also been the subject of many complaints about smells and odours. Benzene, toluene, and trichloroethylene, amongst other VOCs, were measured off-site in small concentrations as shown in Table 2.3 (Klemans et al, 1995; Lakhanisky et al, 1993). Odour complaints again led to the investigation of the Nant-y-Gwyddon landfill in Wales (ENTEC, 1998). Measurements in this community (500-1000 m from the site) found only benzene to exceed the U.K. environmental assessment level (3.24$\mu g/m^3$ for benzene) by factors of up to 6. It was estimated in this investigations that the landfill contributed up to 1.1 ppb (3.6$\mu g/m^3$) of the benzene in the community air samples, the rest probably being contributed by other sources such as motor vehicle emissions. The California landfill testing Program measured 10 VOCs in ambient air at the perimeter of 288 landfills, both hazardous and non-hazardous (Baker et al, 1990). Benzene was detected at 45%, trichloroethylene at 33%, and vinyl chloride at 8% of sites. Maximum concentrations detected are shown in Table 2.3 and again show the highest concentrations in ambient air for benzene.

The studies in Table 2.3 show that measurements taken at the boundary or in the immediate vicinity of the sites are generally higher than average ambient air concentrations (rural and urban) as published by the WHO (World Health Organization, 1998), but lower than the WHO air quality guidelines. For suspected carcinogens (benzene, trichloroethylene, vinyl chloride) the WHO does not recommend safe levels. Benzene in the immediate vicinity of the Mellery and Californian sites exceeded limits proposed by the EC (European Commission, 1998).

Table 2.3: Concentrations of selected volatile organic compounds measured near landfill sites in ambient air

	Concentrations measured near waste sites (? g/m³)			*Average ambient concentrations (? g/m³)*	*WHO air quality guideline (? g/m3)*	*EC ambient air quality limit value (ug/m3)*
Montchanin (France)	*at site, 1.5 m from ground*	*first house (100m)*	*600-700m from site*			
total VOCs	1364	433	193	-	-	
saturated aromatic hydrocarbons	418	302	113	-	-	
halogenated compounds	57	18	4	-	-	
Mellery (Belgium)	*immediate vicinity*	*village of Mellery*				
benzene	152	4.2		1 (rural), 5-20 (urban)	no safe level	5
toluene	190	11.4		< 5 (rural), 5-150 (urban)	260, weekly average	
ethylbenzene	56	2.3		1-100	22,000, 24 hour average	
trichloroethylene	65	2.5		< 1 (rural), <10 (urban)	no safe level	
vinyl chloride	19			0.1-10	no safe level	
tetrachloroethylene	15	1.3		<1 (rural), < 5 (urban)	250	
Nant-y-Gwyddon (Wales)	*1 m above ground*	*in community during odour events*				
total non methane VOCs	59-618	37-490				
benzene		4-17.9		1 (rural), 5-20 (urban)	no safe level	5
California : 288 landfills	*perimeter of landfill max concentration measured*					
benzene	1620			1 (rural), 5-20 (urban)	no safe level	5
trichloroethylene	411			< 1 (rural), <10 (urban)	no safe level	
vinyl chloride	27.5			0.1-10	no safe level	

Levels of volatile organic compounds measured in the nearby communities in Mellery and Nant-y-Gwyddon are within the range of average ambient urban concentrations but in the Nant-y-Gwyddon community benzene exceeds the EC limit. Again, it should be noted that air quality guidelines and limits do not take account of exposure to multiple chemicals. Limits are not available for example for total VOC concentrations.

Indoor air

The migration of landfill gas containing VOCs through soil into basements of houses causing pollution of indoor air has been proposed as a route of exposure of residential populations (Brosseau and Heitz, 1994; Foster, 1993; Lewis-Michl et al, 1998), although very little data is available to judge the importance of this route. Eikmann (1996) summarises results from a German study which found chlorinated VOCs in basements of house 150 m away from a hazardous waste site at higher concentrations than above the landfill surface, as shown in Table 2.4. Concentrations of the 5 VOCs measured within the basements are also higher than average ambient background concentrations (World Health Organization, 1998) (see Table 2.3 for background concentrations). A New-York State study investigated cancer incidence around municipal landfill sites with conditions that allowed for possible indoor human exposure through soil gas (Lewis-Michl et al, 1998). Out of 245 municipal landfills in the state 38 were identified as having potential off-site soil gas migration. For only 3 of these sites indoor sampling results were available, showing no VOC contamination of indoor air in houses near two sites and contamination with vinyl chloride, benzene, and trichloroethane in houses at the third site.

Table 2.4: concentration ($\mu g/m^3$) of VOCs in air at and nearby a hazardous waste site in Germany (from Eikman 1996)

	cellars (150 m from site)	*1.5 m above landfill surface*
trichloromethane	15	3
tetrachloromethane	160	10
trichloroethylene	5100	22
tetrachloroethylene	5000	140
dichloromethane	200	12

Air emissions of compounds other than VOCs

Very little is known about air emissions of toxic compounds other than VOCs, whether through landfill gas emissions or dust and particle emissions. The OTA (Office of Technology Assessment, 1989) reports that mercury has the potential to volatilize into the air and

documents a Swedish study which found mercury levels at four landfills to exceed background levels one to two-fold. Young and Heasman (1985) tested landfill gas at 9 industrial landfill sites for the presence of heavy metal elements and found that none of the 44 elements measured exceeded toxicity threshold. In fact, concentrations in the air above the landfill site were higher for several metals than concentrations in the landfill gas. According to the authors this may indicate that dust rather than landfill gas is the predominant source of heavy metal emissions from landfill sites. Dust emissions were also thought to be a probable explanation of high concentrations of heavy metals found in soil near an incinerator waste dump (Smith and Lloyd, 1986). The National Research Council (1991) reports documented migration of heavy metals into to air at 71 (7%) out of 951 National Priority List (NPL) Sites. Air emissions of other toxic compounds, PCBs, dioxins, pesticides, were each documented at one percent or less of the NPL sites.

2.2.2 Human exposure

Direct measurements of exposure of human populations to chemicals from waste sites include two types of measurements: personal monitoring and biological monitoring (National Research Council, 1991). In personal monitoring the concentration of air contaminants is measured in the breathing zone of the individual, biological monitoring uses markers to measure either the internal dose of chemical (biomarkers of exposure), or of the biological response to exposure (biomarkers of response or early effect) (Hoet and Haufroid, 1997; Vine, 1996).

Biomarkers of exposure measure levels of chemicals in human tissue and fluids (e.g. blood, urine). These techniques can generally only measure a small number of chemicals and their use is limited to situations where environmental monitoring data indicate specific chemicals that are of particular concern. The presence of chemicals in the body is currently difficult and costly to measure.

Biomarkers of response or early effect measure biological responses such as chromosomal changes (sister chromatid exchanges) and molecular changes (DNA adducts), or changes in concentrations of liver enzymes, and could be seen as early effect manifestations. Response biomarkers may be a step in the pathological process towards disease (Vine, 1996), but their interpretation is difficult whilst the link with clinically overt disease remains unclear. For example, Sorsa et al (1992) find structural chromosome aberrations predict cancer risk better than sister chromatid exchanges. They also point out that theoretically it is reasonable to assume that chromosome damage is directly related to cancer aetiology, but that the number of agents clearly shown to induce chromosome

damage in humans is still limited. Increased frequencies of chromosome changes may indicate exposure to mutagens and carcinogens but it is at present not clear how well they predict cancer risk or risk of other outcomes such as congenital anomalies.

Personal monitoring and biological monitoring have been used to measure exposure in occupational settings (Lauwerys and Hoet, 1993), but rarely in studies of environmental exposures (National Research Council, 1991), and even less in the study of waste site exposures. Studies that have directly measured exposures in landfill workers and residents are summarised in Table 2.5.

2.2.2.1 Workers

There are very few published studies of personal or biological monitoring of workers at landfill sites (Johnson, 1997), although monitoring has been recommended as part of medical surveillance programmes of hazardous waste site workers in the United States (Gochfield, 1990).

Personal Monitoring

Bridges et al (1996) used personal monitoring to measure the concentration of 14 selected volatile organic compounds at a waste sites in the U.K. Four waste site employees carried personal samplers for the duration of 4 hours and 40 min on the same day and at the same time, on four separate occasions. All concentrations measured were well below occupational standards, but generally higher than concentrations measured in ambient air samples at fixed locations (2, 5, and 10 m) above the landfill surface (see previous section). Concentrations of some specific chemicals varied greatly between individual workers. For ethylbenzene for example exposures were higher in the drivers than the office workers, whereas for nitromethane higher exposures were found in office workers compared to maintenance staff. The authors conclude that the differing patterns of exposure amongst the workers may indicate that the landfill was not the main source of exposure to these chemicals.

Table 2.5: Studies measuring human exposure to chemicals from waste sites

Reference	*Study site(s)*	*Exposed population*	*Control population*	*Exposure Measure*	*Reported Findings*
Workers					
Bridges, 1996	landfill site in UK	4 workers at waste site		personal monitoring of 14 VOCs	concentrations of all 14 VOCs well below occupational standards.
Hartmann, 1998	waste disposal site in Germany	44 waste site workers	47 controls from local administration	chromosomal aberrations, SCE, DNA damage	higher frequency of chromosomal aberrations and DNA damage in waste site workers, suggesting exposure to genotoxic compounds at waste site; no difference in SCE.
Fender, 1998	2 waste disposal sites in Germany (including above: Hartman et al)	site 1: 43 waste site workers (same as above), site 2: 29 waste site workers	site 1: 47 controls; site 2: 24 controls from local administration	chromosomal aberrations, SCE	higher frequency of chromosomal aberrations, suggesting exposure to genotoxic compounds; no difference in SCE.
Gonsebatt, 1995	hazardous waste landfill site in Mexico	12 waste site workers	7 residents from nearby village	chromosome aberrations, SCE	higher frequency of chromosome aberrations, suggesting exposure to geotoxic compounds, no difference in SCE
Residents					
Hamar, 1996	hazardous waste site in US	100 residents within 3 miles from site	106 residents in community 45 miles away	serum VOCs : 31 VOCs measured, 10 with detectable results	acetone higher in waste site community; 1,1,1-trichloroethane higher in control group. Overall no apparent association.
Reif, 1993	hazardous waste site in US	residents in two areas adjacent to site: 149 in area 1, 172 in area 2	residents in community 12-15 miles away	urine mercury	No statistically significant difference in percentage detectable mercury levels or mean mercury level
Kurttio, 1998	waste treatment plant with incinerator in Finland	11 workers, 45 high-exposure residents (1.5-2 km), 38 medium-exposure (2.5-3.7 km), 30 low-exposure (5 km)	reference population (30 km)	hair mercury	highest absolute mercury levels and increase over 10 year in workers; in residents decreasing mercury levels with distance from site.
Stehr-Green, 1986	3 waste sites in Indiana, US	residents in community near waste sites: 51 high risk, 55 at-risk	8 unexposed residents in community near waste site	serum PCBs	high average level and abnormally elevated PCB levels in both high risk group and at-risk group compared to background levels.
Stehr-Green, 1988	12 waste site communities in US	9-114 residents in each community		serum PCBs	serum levels in majority of communities (10 out of 12) within background range. High levels in 2 communities
Heath, 1984	Love Canal waste site, US	46 exposed residents in houses where chemicals from site had been detected	residents in adjacent census tract	SCE, chromosomal aberrations	no difference in frequency of chromosome changes
Lakhanisky, 1993	hazardous waste site in Mellery, Belgium	51 residents, including 11 children of village with waste site	52 control persons: blood donors	sister-chromatid exchanges (SCE)	higher frequency of SCE in exposed population, in particular children
Klemans, 1995	hazardous waste site in Mellery, Belgium	47 children from village with waste site	children from control community	chromosomal changes	chromosome damage frequency returned to background levels after site remediation.
Clark, 1983	pesticide landfill in Hardeman County	49 exposed residents, 57 unexposed	use of contaminated well water	liver function	abnormalities in liver function in exposed. Returned to normal 2 months later.

Biological monitoring

Hartmann et al (1998) studied exposure of workers at a waste disposal site in Germany by comparing the frequency of structural chromosome aberrations, sister chromatic exchanges and DNA damage between 44 waste site workers and 47 controls working in local administration. Structural chromosome aberrations and DNA damage were more frequent amongst the waste site workers, suggesting that exposure to genotoxic compounds at the waste site occurred. Sister chromatid exchanges did not differ between groups. Smokers were found to have a higher frequency of all endpoints but smoking did not explain the difference between the two exposure groups. A second study combining the study population of the Hartmann study with 39 workers and 24 controls at a second waste site, reports largely similar findings (Fender and Wolf, 1998).

A Mexican study compared cytogenetic markers in 12 hazardous waste landfill site workers and 7 controls from a nearby village (Gonsebatt et al, 1995). Workers had higher frequencies of chromosome aberrations but not of sister chromatid exchanges. Smoking was more frequent amongst controls. A previous study of the workers and controls had found no differences in blood lead, urinary mercury, cadmium in hair, or phenols on blood and urine (Gonsebatt et al, 1995). Only arsenic was found to in higher concentrations in urine of workers than in controls. The authors conclude that although chromosome damage could not be attributed to a particular chemical exposure, it did indicate exposure to genotoxic chemicals. The number of subjects in this study is small however, and the selection of the control population unclear.

2.2.2.2 Residents

Biomonitoring of residents near waste sites has included the use of biomarkers of exposure (volatile organic compounds in blood, PCBs in blood, and mercury in hair and urine) and biomarkers of response or early effect (cytogenetic monitoring / liver function tests) (Table 2.5).

Biomarkers of exposure

Hamar et al (1996) measured volatile organic compounds in the blood of residents near a National Priority List Site in the U.S. Several factories and a hazardous waste treatment facility which operated hazardous waste incinerators, were located at the site. On-site monitoring showed high levels of organic compounds in the soil and groundwater but no off-site contamination of groundwater or air had been documented. One hundred blood samples of randomly selected residents from the community near the site (within 3 miles) were

compared with 106 blood samples of residents from a control area with similar age distribution, social class, and housing characteristics as the waste site community. Blood samples were analysed for 31 compounds, but only 10 of these were detected in enough samples to allow for comparisons between the waste site area and the control area. Levels of acetone were statistically significantly higher in the blood samples of the waste site community than the control community, levels of trichloroethane significantly lower. Of the other compounds five (benzene, styrene, ethylbenzene, *m,p*-xylene, *o*-xylene) showed lower and three (2-butanone, 1,4-dichlorobenzene, toluene) showed higher levels in the waste site community but none of these differences were statistically significant. Levels of 8 of the 10 VOCs were below those of a national reference population, 1,4-dichlorobenzene and 2-butanone levels were slightly higher than the national reference in both the waste site community and the control community. VOCs do generally not bio-accumulate so the study measured current exposure only, not past exposures. The authors conclude that it is feasible to monitor for VOC exposure in waste site communities but that such monitoring should be carried out only where environmental monitoring has indicated high levels of VOCs.

Mercury concentrations in urine samples of residents of two areas adjacent to a U.S. National Priority List Site were compared to samples of residents living in a comparison area 12-15 miles away in a study by Reif et al (1993). The site was contaminated with volatile compounds, organochlorine pesticides and heavy metals. Urine mercury levels provide a measure of medium-time exposure: mercury takes several months to excrete. The percentage of people with detectable levels of urine mercury was higher in one of the two areas near the site than the control area (8.7% vs. 5.4%), although this difference was not statistically significant (OR 1.9 95% CI 0.6-5.8). Mercury levels in the other adjacent area did not show any differences with the control area. Demographic differences, between the populations were taken into account as were other possible sources of mercury exposure such as dental fillings. Mercury levels in all three areas were generally within the reference range of the general population. The percentage of subjects having detectable mercury levels was small (7% overall), due, according to Kurttio et al (1998), to the mercury detection limit in this study being too high.

Kurttio et al (Kurttio et al, 1998) studied hair mercury concentrations of a population living near a hazardous waste treatment plant in Finland, which included an incinerator. The same population had been studied 10 years earlier, at the start of the plant. The investigators chose mercury as the main compound for study because elevated concentrations of mercury, but not of other pollutants, had been measured in the environment (ground and surface water) surrounding the plant. Increases in hair mercury concentrations over the 10

year period were found in each of 5 study groups: workers at the plant, high-exposure residents (1.5-2 km), medium-exposure residents (2.5-3.7 km), low-exposure residents (5 km), and a reference group living 30 km away. The change in mercury concentration was highest for workers at the plant, followed by the high-exposure resident group, and was lowest in a reference population 30 km away. Absolute concentrations were highest again in the workers followed by the high and medium exposed residents, and lowest in the low-exposure residents and the reference population. Fish consumption was highly associated with hair mercury levels but did not explain the differences between the exposure groups. The levels of mercury in all exposure groups were generally within the range of typical levels in the general populations: only 3 individual measurements (one from high-exposure group, one from low-exposure group, one from reference populations) exceeded this range.

A pilot study in Indiana, U.S., assessed the use of serum PCB monitoring in a community where 3 waste sites were located (Stehr-Green et al, 1986). PCB contamination had been detected at the sites. PCBs bio-accumulate in body tissues and serum levls reflect long-term exposures. A high exposure group was selected on the basis of reported activities of nearby residents leading to potential of exposure to the 3 sites (occupation, swimming, fish eating, playing on-site, etc). The non-exposed group comprised residents of the same community who reported no potential exposure. In addition an 'at-risk' group was selected randomly from residents within 0.5 mile of the site. Serum PCB levels were higher in the high exposure group and the 'at-risk' group than in the unexposed group, but differences were not statistically significant after exclusion of occupationally exposed individuals. Levels in the high-exposure and 'at-risk' group were higher than levels measured in general U.S. populations measured previously but this may be due to the inclusion of occupationally exposed individuals in the study. The absence of an unexposed control population makes the elevated PCB levels in this community difficult to interpret.

The same investigators report serum PCB levels in 12 communities near waste sites throughout the U.S. where PCB contamination on or off-site had been documented, including the above community in Indiana (Stehr-Green et al, 1988). In 10 of the twelve communities the percentage of subjects with high levels of PCBs (>20 ppb) were reported to be within the background ranges found in other population-based studies. In two communities, including the Indiana community, the percentage of subjects with PCB levels of over 20 ppb was statistically significantly higher than expected on the basis of the population-based studies. The study does not take account of demographic factors or possible other exposures which may explain differences in PCB levels found between the twelve waste site communities and comparison populations.

Biomarkers of early effect

Heath et al (1984), compared the frequency of chromosome changes (sister-chromatid exchanges and chromosomal aberrations) in residents who lived in the first ring of houses adjacent to Love Canal in 1978 with control persons from socio-economically similar census tracts. No difference in frequency of chromosome damage was found. Chromosome changes were measured in 1981 and 82, a few years after people were evacuated from the first ring of houses and therefore no longer exposed. The authors point out that chromosome damage may be a reversible effect, which may explain the negative findings.

In Mellery, Belgium, gases containing a complex mixture of volatile organic compounds escaped when the clay seal of a landfill site cracked. Because some of the detected chemicals were known mutagens and/or carcinogens, damage to chromosomes was studied and an increase in chromosome damage (sister chromatid exchanges) was found among Mellery residents but not in unexposed subjects in subgroups of both smokers and non-smokers (Lakhanisky et al, 1993). In children aged 8-15 a more marked difference was found between exposed and unexposed groups than among adults. The findings indicated exposures similar to those of occupationally exposed populations. The adult unexposed comparison subjects were recruited from a volunteer blood donors list and may therefore have comprised a group with different risk behaviour and exposure to possible risk factors for chromosome damage than the general population. The blood donors reported less 'occupational exposure' than the Mellery inhabitants. It is unclear how occupational exposure was defined and results have not been adjusted for it. A follow-up study after site remediation reduced the concentration of the atmospheric pollutants to background levels, reported that chromosomal damage in Mellery children had returned to background levels and were no longer different from unexposed populations (Klemans et al, 1995).

In Hardeman County, Tennessee, well water used as drinking water by residents was found to be contaminated with high concentrations of carbon tetrachloride and other chlorinated compounds after complaints were received about the taste of the water. A nearby landfill where 300,000 barrels of pesticide waste had been buried was found to be responsible for the contamination. Analysis of indoor air and bathroom air while showers were running both indicated detectable levels of carbon tetrachloride and other organic compounds in houses that received water from the contaminated wells. Carbon tetrachloride has been identified in toxicological studies as a strong liver toxin and the investigation carried out several months after the population had stopped using the water for drinking, showed abnormally high levels of liver enzymes (indicating liver damage) in residents who had used contaminated water

compared to unexposed controls (Clark et al, 1982). The authors concluded that this would have mainly resulted from exposure due to washing and toilet water uses, and possible from previous exposure through drinking and cooking. Two months later, when use of the well had completely stopped, liver function in the exposed population had returned to normal. This study benefited from relatively well-documented exposure information and a clear hypothesis about the possible health effects (i.e. liver disease) related to exposure to carbon tetrachloride.

2.2.3 Summary and conclusions

The presence of toxic chemicals in landfill leachates and gases has been demonstrated in a number of site investigations in Europe and the U.S. The Superfund programme has followed a systematic approach, investigating releases at large numbers of sites to decide on their inclusion on the National Priority List (NPL) with priority for clean-up. NPL sites have been relatively well assessed with respect to the potential or actual migration of hazardous chemical substances from the sites through ground water, surface water, and air (National Research Council, 1991).

It is difficult to describe which toxic chemicals are typically present in landfill leachate. Studies of particular landfills at particular stages can not easily be extrapolated to predict the composition of other landfill leachates. Groundwater studies have documented releases of leachate from waste sites. Compounds most commonly associated with such releases appear to be chlorinated and aromatic hydrocarbons, and heavy metals. Little is known however about the transport of these specific compounds in groundwater and it is not possible to say to what extent attenuation processes may restrict transport of compounds further away from sites. Groundwater pollution plumes have at particular sites been found only to extend to the immediate vicinity of sites, while at other sites plumes have been transported hundreds or even thousand of metres from landfills. Findings at particular sites and at particular times can not be used to draw conclusions about the distance to which pollution plumes may extend at landfill sites in general. Where drinking water wells are located within the reach of a landfill pollution plume human populations are at obvious risk of exposure to chemicals from landfills. A few incidents of drinking water pollution from waste sites have been reported in the U.S., with concentrations of toxic chemicals exceeding drinking water guidelines. The chemicals of concern in these cases have been chlorinated and aromatic hydrocarbons.

Landfill gas contains volatile organic compounds as trace components. The range of volatile organic compounds found in landfill gas does not appear to vary substantially between different sites, although concentrations of these compounds do. Concentrations of specific VOCs detected within undiluted landfill gas have at some sites reported to exceed occupational exposure limits. Aromatic (benzene, toluene) and chlorinated (vinylchloride, tetrachloroethylene) hydrocarbons are amongst these. Landfill gas is likely to be substantially diluted in ambient air as soon as it is released from the landfill surface. Little is known about possible concentrations of substances in ambient air at distances away from landfills where exposure of residents may occur. From the few published findings of ambient air monitoring near landfill sites, concentrations of VOCs appear in the immediate vicinity of sites to be higher than average ambient air concentrations, but lower than WHO air guidelines. In villages near, but at unknown distances from, two European landfill sites where ambient air measurements were taken, concentrations of individual VOCs tended to be within the range of average ambient urban concentrations. Little is known about whether, when individual compounds do not exceed health limits or average levels, the concentration of the total mixture of VOCs may be important. Monitoring of landfill gas and ambient air near landfills has been limited mainly to volatile organic compounds and data about the presence of other toxic chemical compounds, for example heavy metals, in gas, dust, or particulate emissions from sites, is almost completely lacking.

Exposure of humans to chemicals from landfill sites is difficult to measure, not only because direct exposure monitoring is costly, but also because exposures are likely to be to unknown and complex mixtures of chemicals which makes it extremely hard to find appropriate measures. Personal monitoring and biomarkers of exposure are generally useful only when specific chemicals of particular concern have been identified through environmental monitoring. Also, in both personal and biological monitoring, landfill exposures are hard to distinguish from other environmental exposures. Confounding by other sources of exposures is difficult to measure and therefore difficult to control for in these measurements. Studies which have employed direct exposure measurement to assess exposure to landfills in humans have been few. Chromosome studies of workers at waste sites in Germany and Mexico have suggested exposure of these workers to genotoxic chemicals. An increased presence of chromosome changes was also reported in children resident near a landfill site in Mellery, Belgium, but not in Love Canal residents which may have been due to reversibility of chromosome damage. Findings in Mellery children returned to normal after closure of the landfill, also indicating a reversible effect. In Hardeman County exposure to waste site pollutants in drinking water was measured by changes in levels of liver enzymes.

This study showed that exposure was likely and resulted in reversible changes in liver function.

Biological monitoring of mercury, PCBs, and VOCs in populations near landfill sites has not convincingly shown exposure to these compounds to be higher in populations near sites than in control areas. Studies are difficult to interpret since they generally measure only one compound of a range of possible contaminants that may have been released by the particular landfill. A Finnish study found some evidence for mercury levels being higher in hair of residents living closer to a hazardous waste treatment plant. In this study however, mercury levels in this study, even if due to the treatment plant, were low, lower than levels reported in general reference populations.

In summary, toxic chemical compounds have been found to be present in landfill gas, leachate, and off-site contamination at particular landfill sites. Halogenated and aromatic hydrocarbons have raised most concern, both in water contamination and in air emissions from landfills. Concentrations of these compounds in environmental media surrounding landfills may be high in the case of drinking water contamination. Concentrations in ambient air may be relatively high in the immediate vicinity of sites, but have been reported to be within normal rural and urban ranges in residential communities near the few sites where such investigations have been carried out. Exposures in human populations are difficult to measure. Direct exposures studies are scarce and have generally tended not to find strong evidence for exposure of residents near waste sites.

2.3 TERATOGENIC POTENTIAL OF CHEMICALS FOUND IN LANDFILL SITE CONTAMINATION

Many chemicals commonly present in landfill sites have shown teratogenic and/or mutagenic properties and could therefore affect embryonic development and cause congenital anomalies. The current section aims to give a brief overview of evidence from both experimental and epidemiological literature for teratogenic potential of the main groups of chemicals which may be of concern in waste sites exposures. Where possible I have based this section on existing reviews.

It would fall beyond the scope of this thesis to review in depth the evidence for teratogenicity and mutagenicity of every chemical that may be present in landfill sites. At hazardous waste sites investigated under the Superfund programme in the U.S. more than 2,000 individual substances were found in contaminated environmental media (DeRosa et al, 1996). From section 2.2 it became clear that very little data is available to indicate which specific chemicals are mainly present in landfill exposures. Volatile organic chemicals have attracted most concern. Evidence from the U.S. Superfund programme has shown which chemicals are commonly detected in completed exposure pathways from hazardous waste sites (Johnson and DeRosa, 1997) (Table 2.6). I have limited this section to chemicals shown in Table 2.6, which fall in the following main groups: industrial organic solvents, chemicals used in the plastics industry (mainly vinyl chloride), heavy metals, and PCBs. Other groups of chemicals which may be present in hazardous waste landfill sites but are, to our current knowledge, not commonly present in off-site contamination from sites, include pesticides, dioxins and furans, phthalates, and poly-aromatic hydrocarbons (PAHs). Extensive reviews of the teratogenicity of environmental and industrial chemicals including these groups of chemicals, can be found elsewhere (Barlow and Sullivan, 1982; Couture et al, 1990; Garcia, 1998; Schardein, 1985).

This section starts with a discussion of general principles of teratogenesis and issues common to the interpretation of teratogenic evidence presented further in the section.

Table 2.6: Substances commonly found at hazardous waste sites in the U.S. (from Johnson 1997)

substances found in completed exposure pathways at > 10% of 530 NPL sites	% of sites	chemical group
trichloroethylene	40	organic solvents - halogenated
lead	34	heavy metals
tetrachloroethylene	30	organic solvents - halogenated
arsenic	23	heavy metals
benzene	21	organic solvents - aromatic
cadmium	17	heavy metals
chromium	17	heavy metals
1,1,1-trichloroethane	16	organic solvents - halogenated
PCBs	15	PCBs
1,1 dichloroethene	14	organic solvents - halogenated
chloroform	14	organic solvents - halogenated
1,1-dichloroethane	13	organic solvents - halogenated
vinyl chloride	13	plastic chemicals
zinc	12	heavy metals
mercury, metallic	12	heavy metals
1,2-dichloroethane	12	organic solvents - halogenated
methylene	12	organic solvents - aliphatic
toluene	10	organic solvents - aromatic

2.3.1 Principles of teratogenesis

A teratogen is an agent that causes defects of fetal development (Harbison, 1980). Traditionally, structural congenital malformations were considered the main manifestation of teratogenic impact, but the term teratogen now also includes agents that induce metabolic, functional, and behavioural defects prenatally in the developing fetus (Wilson and Fraser, 1977).

Environmental agents may cause malformations in the developing embryo through teratogenic and/or mutagenic action. Mutation is by some authors discussed as one of the mechanisms of teratogenesis (Harbison, 1980; Wilson and Fraser, 1977). The term teratogenesis has classically been reserved for effects from post-conceptional maternal exposures, whereas mutagenic action may take place both *before* conception, through exposures damaging the genetic material of maternal and paternal germ cells, and *after* conception through maternal exposure damaging genetic material of somatic cells in the developing embryo. *Post*-conceptional somatic cell mutations in the early embryo may cause congenital malformations and spontaneous abortion (Harbison, 1980; Hemminki et al, 1980), and may play a role in the causation of cancer after birth as in the case of DES exposure (Autrup, 1993; Fraumeni, 1974; Hemminki et al, 1980). Maternal and paternal germ cell

mutations from *pre*-conceptional exposures that could lead to congenital abnormalities in the developing embryo include new single-gene mutations and structural and numerical chromosomal abnormalities (Dellarco, 1993; Favor, 1993). Only autosomal dominant and some recessive X-linked single gene mutations in germ cells can lead to detectable malformations in the offspring. Interest in paternal exposure leading to malformations in the offspring through so-called 'male-mediated teratogenesis' is increasing, although evidence in humans remains scarce (Olshan and Faustman, 1993; Sever, 1995).

In the 1970s Wilson and Fraser (1977) discussed the main principles of teratogenesis which have changed little since. Wilson and Fraser described how the teratogenic response of a chemical was defined, besides the nature of the specific chemical, by the developmental stage at the time of exposure, the dose of the teratogen, and the susceptibility of species and genotype to the given teratogen.

Developmental stage

The susceptibility of the developing embryo or fetus to the action of a teratogen varies according to the stage of development. There are three major stages in development: the pre-implantation period (week 1-2), the embryonic period (3-8 weeks), and the fetal period (9 weeks onwards) (Moore and Persaud, 1993). Major structural malformations may be produced during the embryonic period when tissues and organs are formed. Teratogenic impacts in the other periods are more likely to lead to death of the embryo (pre-implantation period), or minor malformations, growth retardation, and functional defects (fetal period) (Harbison, 1980; Wilson and Fraser, 1977). Recently, experimental evidence has shown that structural malformations may also be produced during the pre-implantation period (Kimmel et al, 1993).

Within the embryonic period, each organ has a critical period during which exposure to a teratogen may cause abnormal development. The type of congenital malformation produced depends on which organs, or parts of organs, are susceptible at the time of the exposure (Wilson and Fraser, 1977). Development of the heart and central nervous system for example start early, in week 3, whereas development of the palate does not start until week 6-7 (Moore and Persaud, 1993). A teratogenic insult in week 3 will therefore not produce cleft palate, but may produce a heart or central nervous system defect. The timing of the impact may determine the severity of the malformation: a teratogen acting early in the development of the eye for example is likely to produce a more serious malformation than one acting when the formation of the eye is almost completed.

Dose

An increasing dosage of a teratogen generally leads to an increase in the incidence and in the severity of defects produced (Brent, 1986). Most evidence suggests that teratogens have a threshold below which teratogenic effects are not produced (Brent, 1986; Harbison, 1980, Wilson, 1977 #1546), although there has been some discussion as to whether this threshold dose exists for teratogens acting through a mutagenic mechanism (Gaylor et al, 1988; Giavini, 1988). For outcomes such as mutations and cancers it is widely accepted that they result from stochastic events and could therefore be produced at any dose, however low it may be. In this concept risk declines with decreasing doses but never theoretically disappears, although it may approach the background risk level in a population and therefore not be detectable in population based studies. Threshold doses for teratogens have been established in experimental research, but threshold doses in humans are very hard to extrapolate from experimental data. It is not known in which dose environmental chemicals, for example in potential landfill exposures, may be "safe" for humans.

Species and genotype

The response to a teratogen differs between species. The thalidomide experience for example has shown that the same chemical may produce malformations only in certain species (Janerich and Polednak, 1983). It is difficult to extrapolate experimental animal data to humans because animal species and humans vary in a number of ways including toxicocinetics, toxicodynamics, placental characteristics, and embryonic and fetal sensitivity to chemicals. Hemminki and Veneis (1985) show that several chemicals, in particular ethanol, methyl mercury and PCBs, have produced malformations in experimental animals at effective doses close to the human effective doses, although different malformations were produced in different animal species and humans. For many chemicals there is insufficient data about teratogenic effects in humans to make this comparison. It is therefore often not possible to assess how well effects in animal experiments predict effects in humans. The general belief is that practically all chemicals will ultimately produce some kind of adverse effect when given in a high enough dose to a pregnant animal (Barlow and Sullivan, 1982). If adverse effects are observed in experiments at doses which are clearly not toxic to the mother or when a chemical induces specific malformations, this is taken to suggest teratogenic potential in humans (Barlow and Sullivan, 1982).

In addition to differences between species, genotype within a species may determine susceptibility to teratogenic insults. Genetic differences in the response to teratogens have been shown in experimental animals and humans (Moore and Persaud, 1993). The term

'multi-factorial' is used for the causation of malformations by a combination of environmental and genetic factors (Fraser, 1976). A large proportion of malformations is thought to have a multi-factorial aetiology.

Interactions

The evaluation of effects of human exposures to environmental teratogens, whether from landfills, at the work place, or elsewhere, is complicated by the fact that exposures are characteristically to mixtures of different chemicals. Possible interactions of chemicals may occur within a mixture, which means that the biological effects of one compound are altered by another (Skalko, 1985). Interactions of two or more chemicals can result in additivity (combined effect is the sum of the individual effects), antagonism (combined effect is significantly less than the sum of the individual effects), synergism (combined effect is significantly greater than sum of the individual effects), or potentiation (one agent does not have an effect but when given in combination it has) (Nelson, 1994). Nelson (1994), in a review of studies on interactions in developmental toxicology, concludes that in about one third of the reports no interactive effects were found, in one third antagonistic effects, and in another third potentiative or synergistic effects. As an example of the latter effect, caffeine has been shown to increase the production of cleft palate in mice after X-ray exposure, whilst not being teratogenic alone as a single exposure (Skalko, 1985; Yielding, 1993). A study investigating the interactions of genotoxic chemicals present in hazardous waste sites (lead tetra-acetate, arsenic trioxide, dieldrin, tetrachloroethylene), found both antagonistic (mixtures of lead tetra-acetate and arsenic trioxide) and synergistic (dieldrin and tetrachloroethylene) effects of different combinations of chemicals, and concluded that effects of individual chemicals may not be true predictors of the interactive effects of complex chemical mixtures (Ma et al, 1992).

Research on interactions of chemicals is complex and although experimental data is increasingly becoming available (Teuschler and Hertzberg, 1995), effects of multiple chemical exposure in humans are almost entirely unknown (Tardif et al, 1992).

2.3.2 Organic solvents

Solvents are organic chemical compounds used to dissolve, suspend, or change the physical properties of other materials (Valciukas, 1994). Solvents include aliphatic hydrocarbons (heptane, hexane, cyclohexane), halogenated hydrocarbon (trichloroethylene, tetrachloroethylene, chloroform), aromatic hydrocarbons (xylene, toluene, benzene), and aliphatic alcohols, glycols and glycol ethers. Solvents are used in many different industries

(Table 2.7) and can be found in dry-cleaning products, anaesthetics, and many common household products such as spray adhesives, spray paints, inks, dyes, glues, and petrol.

Table 2.7: The use of organic solvents in various industries (adapted from Suess and Huismans, 1983, and Tardif et al 1992)

Use	*Organic solvent*
Formulation of adhesives	Ketones, aliphatic and aromatic hydrocarbons
Formulation of cleaning materials and polishes	Aliphatic hydrocarbons
Formulation of pesticides	Aliphatic hydrocarbons
Degreasing of fatty skins in tanning	Aliphatic hydrocarbons
Extractive industries, e.g. essential oils	Alcohols and aliphatic hydrocarbons
Manufacture of food flavourings, essences and toiletries	Glycols, alcohols and glycol esters
Photographic industry	Alcohols, ketones, and glycol esters
Reaction media in the pharmaceutical industry	Hydrocarbons, alcohols, esters, halogenated solvents and others
Metal cleaning	Halogenated solvents
Dry cleaning	Halogenated solvents
Paint industry	Aromatic hydrocarbons (toluene, xylene), glycols

In general, organic solvents have a high volatility and low solubility. Many of the volatile organic compounds detected in landfill gas (section 2.2) are part of the family of 'organic solvents'. Relatively soluble solvents can be present in groundwater. For example, some low molecular weight chlorinated hydrocarbons (trichloroethylene, 1,2-dichloroethane, 1,1,1-trichloroethane) have been found frequently as organic groundwater contaminants (Anderson et al, 1983; Rivett et al, 1990).

Many organic solvents are teratogenic or embryotoxic in animals, depending on the specific solvent and the particular animal species (Brown Woodman et al, 1994; Hardin, 1983; Schardein, 1985). Toluene has generally not produced structural malformations in experimental animals although growth and skeletal retardation has been a common finding (Wilkins-Haug, 1997). Similarly, benzene has consistently been shown not to be teratogenic below maternal toxicity levels, but has shown fetal growth retardation (Barlow and Sullivan, 1982). Trichloroethylene has specifically been related to cardiac defects in different animal species (Dawson et al, 1990; Loeber et al, 1988). Several organic solvents including benzene, ethylene dichloride, methyl chloroform, toluene, and trichloroethylene have shown mutagenic effects (Barlow and Sullivan, 1982).

Information about the effects of solvent exposure on pregnancy in humans comes mainly from case reports after solvent abuse, occupational studies, and studies on the effects of exposure to organic solvents in drinking water.

Case reports of solvent abuse

A number of case-reports have described effects of abuse of solvents, in particular toluene, during pregnancy (Donald et al, 1991; Hersh et al, 1984; Toutant and Lippmann, 1979). Toluene abuse through sniffing of glue and other substances has produced a syndrome with similar features to the fetal alcohol syndrome, including microcephaly, central nervous system dysfunction, craniofacial and limb defects and growth retardation. In at least half these reports toluene was the only exposure reported (Wilkins-Haug, 1997) so it seems unlikely that other drug exposures, alcohol, smoking were responsible for the effects found. The levels of toluene exposure achieved through glue sniffing and other such abuse are extremely high, higher than in most occupational and environmental situations (Wilkins-Haug, 1997).

Occupational exposure to solvents

Exposure to solvents may occur in a variety of occupational settings including dry cleaning, painting, printing, laboratory work, medical work, rubber manufacturing. There have been a number of reviews of effects of parental occupational exposures and adverse pregnancy outcomes (Lindbohm, 1995; Roeleveld et al, 1990; Rosenberg et al, 1987; Sever, 1994; Taskinen, 1990). These reviews report inconsistent findings regarding the relationship between congenital anomalies and solvent exposures and occupations involving solvent exposure. Exposure measurements are generally based on surrogate measures, often job titles, and very rarely on personal or biological monitoring. Solvent exposures estimated from a variety of job titles have been found to be related to oral clefts, neural tube defects, and cardiac malformations in more than one study, although the absence of such relationships has also been reported (Sever, 1994; Taskinen, 1990). Studies generally have more statistical power to detect increases in the risk of these relatively common malformation groups than in the risk of rarer anomalies. Other, less common, groups of defects, including digestive system anomalies, abdominal wall defects (gastroschisis and omphalocele), intestinal agenesis, and urinary anomalies, have been related to occupational solvent exposure, but generally in single studies only (Sever, 1994; Taskinen, 1990). The Baltimore-Washington Infant study, a large case-control study of over 3,000 cardiac anomaly cases, found little evidence of a relationship between solvent exposure and the total group of cardiac defects (Ferencz et al, 1997). However, odds ratios of more than 3 were found for

some specific defects including transposition of the great arteries and hypoplastic left heart. This shows the potential importance of studying specific defects rather than large, heterogeneous groups.

The majority of studies investigate exposure to organic solvents as one group of chemicals, not distinguishing between different types of solvents. Specific relationships have been found between aromatic solvents and all congenital defects and urinary defects (McDonald et al, 1987), tetrachloroethylene and spontaneous abortions (Kyyronen et al, 1989), glycol ethers and oral clefts, neural tube defects and multiple anomalies (Cordier et al, 1997). Specific occupations that have been implicated are laboratory work, work in pharmaceutical industry, and dry cleaning (Lindbohm, 1995; Roeleveld et al, 1990; Taskinen, 1990). Down syndrome has been reported to be associated to occupations that may involve solvent exposure: janitors, mechanics, farm workers, metal workers, and food processors (Olshan et al, 1989). Other chemical exposures (mainly heavy metals and pesticides) are likely also to occur in these occupations.

Most of the above findings were reported in case-control studies collecting exposure information through maternal interviews and questionnaires so recall biases may play a role (Sever, 1994). Cohort studies have rarely been feasible to conduct. A recent cohort study of women occupationally exposed to organic solvents reported a large (13-fold) and statistically significant increase in the risk of all major congenital malformations combined (Khattak et al, 1999). The number of cases of congenital malformation in the exposed group of women (n=125) was 13, in the non-exposed group (n=125) one malformation occurred. Congenital malformations in the exposed group included neural tube defects (2), cardiac defects (2), renal abnormalities (2), diaphragmatic hernia (1), micropenis (1), other central nervous system defect (1). The group also contained four cases however, which would generally not be considered major malformations (laryngomalacie (2), inguinal hernia, and clubfoot). Information on congenital malformations was obtained from maternal interviews so reporting bias may have occurred, explaining some of the increased risk found.

A recent meta-analysis of 5 studies of first-trimester solvent exposure and risk of congenital anomalies calculated a statistically significant odds ratio for major malformations (1.64; 95% CI 1.16-2.30) (McMartin et al, 1998). Groups of malformations studied were different in the 5 studies, and varied from cardiac defects only to all major malformations combined. Also, little definition was given of how different studies measured 'solvent exposure'. One of the five studies measured styrene exposure only. The pooled analysis of five studies with essentially different outcomes and different exposures is questionable. The absence of any consideration of confounding factors makes the study even more difficult to interpret.

Occupational exposure of the father to solvents has been found to be related with an increased risk of spontaneous abortions (Taskinen et al, 1989), and pre-term births (Kristenen et al, 1993), but not with congenital malformations (Kristenen et al, 1993; Taskinen et al, 1989).

Solvent contamination in drinking water

Several studies have investigated reproductive effects of maternal exposure to solvents in drinking water, either from chlorination of drinking water or from pollution by industrial or waste disposal activities. Studies of contamination of drinking water directly linked to waste disposal sites are discussed in detail in section 2.4.3.4. Studies of pregnancy outcomes in relation to water chlorination by-products have been reviewed by Reif et al (1996). Chlorination by-products are halogenated solvents, predominantly trihalomethanes (THM): chloroform, bromodichloromethane, dibromochloromehtane, and bromoform. The review reports on four studies, two of which study birth defects (Aschengrau et al, 1993; Bove et al, 1995). The odds ratio for all birth defects in both these studies is 1.5, comparing respectively municipalities with high levels of THMs in the water supply (Bove et al, 1995) and municipalities with chlorinated water supply (Aschengrau et al, 1993) with unexposed municipalities. The study by Bove (1995) also investigated sub-groups of malformations and found statistically significant increases in the risk of central nervous system defects, major cardiac defects and oral clefts for exposure to THMs. No other malformation sub-groups were studied. Central nervous system defects showed a dose-response relationship with the level of THMs in the drinking water supply. The investigation of other adverse pregnancy outcomes in the four studies showed low birthweight (Bove et al, 1995; Kramer et al, 1992; Savitz et al, 1995), growth retardation (Bove et al, 1995; Kramer et al, 1992), and still births (Aschengrau et al, 1993) to be associated with THM concentrations or water chlorination (Reif et al, 1996). Reif et al (1996) discuss exposure assessment as the major weakness in the studies, since in all studies water supply of whole communities was used as a proxy of the intake of chlorination by-products by individual mothers, assuming for example that mothers did not use private wells or water filtration systems, or drank bottled water.

2.3.3 Plastic chemicals (vinyl chloride)

Chemicals used in the manufacture of plastics, vinyl chloride, vinylidene chloride, and styrene, are volatile organic compounds and have the potential of being emitted into the atmosphere when present in a landfill site. Vinyl chloride has been detected in landfill gas (section 2.2).

There is no evidence for teratogenic or embryotoxic effects of vinyl chloride and both vinylidene chloride and styrene are teratogenic and embryolethal only at doses toxic for the dam (Barlow and Sullivan, 1982; John et al, 1994). Styrene, vinyl chloride, and vinylidene chloride are mutagenic in test organisms (Barlow and Sullivan, 1982).

Studies on reproductive effects of vinyl chloride and styrene in humans concentrate on genetic anomalies via mutagenic effects of these chemicals. Both vinyl chloride (Fabricant and Legator, 1981; Infante et al, 1976) and styrene (Barlow and Sullivan, 1982) have shown mutagenic activity in humans. Spontaneous abortions and birth defects could be caused by pre-conceptional, mutagenic effects, such as chromosomal breaks, gaps and rearrangements. Increases in chromosomal damage have been reported in lymphocytes of workers exposed to vinyl chloride monomer (VCM) and styrene (Barlow and Sullivan, 1982; Funes-Cravito et al, 1975; Hogstedt et al, 1979). Literature on adverse pregnancy outcomes after maternal or paternal occupational exposure is scarce. A study by Infante et al (1976) compared pregnancy outcomes in wives of VCM polymerisation workers with controls and reported increased fetal death rates for pregnancies occurring after exposure. In a Finnish study work in styrene industry was related to incidence of spontaneous abortions (Hemminki et al, 1980), but in other studies neither spontaneous abortions (Harkonen and Holmberg, 1982) nor congenital malformations (Harkonen et al, 1984) were related to occupational styrene exposure.

A number of studies have investigated reported clusters of congenital malformations, in particular central nervous system defects, in areas where PVC polymerisation plants were located in the U.S. and Canada (Centre for Disease Control, 1975; Edmonds et al, 1978; Edmonds et al, 1975; Rosenmann et al, 1989; Theriault et al, 1983). Most of these studies reported no association between distance of residence to the vinyl chloride plants or parental occupation in the plants and risk of congenital malformation. Rosenmann et al (1989) found a non-statistically significant trend of decreasing risk of central nervous system defects with increasing distance from two plants in New Jersey.

2.3.4 Heavy metals

Heavy metals are found in the environment in a variety of chemical states, as inorganic and organic compounds. The toxicity of metals greatly depends on their chemical state(Wade et al, 1993) which is why both the form in which they are deposited in landfills and

transformations that may affect them in the environment importantly determine the hazard they pose to human health. Metallic compounds are often deposited in landfills as sludges containing relatively insoluble oxides, hydroxides, phosphates, etc. (Department of the Environment, 1978). The main hazard associated with disposal of such wastes is the possible release of metal ions in high concentrations to leachate and possibly to ground and surface water (Department of the Environment, 1978). Chemicals like cyanide and acid wastes can cause dissolution of metal sludges and increase the potential of metals to be transported by leachate or runoff (Department of the Environment, 1978). Some metals, for example mercury (see also section 2.2.1.2) are prone to volatilisation as metallic vapours. Other metals, for example cadmium, are found in the air mainly bound to particles(Wade et al, 1993).

The following metals have been found to cause adverse effects for the offspring when given to pregnant animals: aluminium, arsenic, boron, cadmium, chromium, copper, gallium, indium, lead, lithium, manganese, mercury, nickel, selenium, strontium, tellurium, thallium, and zinc (Barlow and Sullivan, 1982; Chang et al, 1980; Domingo, 1994; Schardein, 1985). Often no mention is made of maternal toxicity so it is not always known whether adverse effects occurred at doses below maternal toxicity. Of the above metals lead, mercury, cadmium, and arsenic and chromium have the greatest significance in terms of their teratogenic potential and/or potential landfill exposures.

2.3.4.1 Lead

Lead has been used in petrol, paints, pipes and plumbing materials, glazing and pottery, batteries, ammunition, flashings, etc. (Wade et al, 1993). The use of lead based residential paints is now banned in many countries and leaded petrol is being phased out. A large amount of lead still enters municipal and hazardous landfill sites from a variety of sources, lead batteries being an important one (Hutton and Symon, 1986; Wade et al, 1993). Particulate lead in the atmosphere originates from a variety of sources including vehicle exhausts, combustion of waste, coal and oil, smelters, and battery and cement manufacturing (Wade et al, 1993). Lead leaching into the water supply from old lead piping may be an important source of lead in drinking water (Bound et al, 1997).

The teratogenicity of lead is discussed in several review papers (Chang et al, 1980; Domingo, 1994) and books (Barlow and Sullivan, 1982; Schardein, 1985). Evidence for lead teratogenecity from experimental studies is inconsistent. In rats gross malformations have

generally not been reported although fetal resorption and general growth retardation may occur at relatively high dosage. A few studies have reported malformations in mice, hamsters and some other animal species after lead exposure. Barlow and Sullivan (1982) conclude that teratogenicity of organo lead compounds is not found in experimental studies, even at doses close those lethal for the dam. Data on mutagenicity of lead has been reported to be inadequate to draw conclusions (Barlow and Sullivan, 1982).

Early observations have reported spontaneous abortions in humans as a result of lead exposure (Chang et al, 1980) and lead oxide has even been used to induce abortions (Schardein, 1985). For low, environmental, lead exposures no firm links with spontaneous abortions have been found, however. Several reviews of lead teratogenicity have concluded that evidence for lead exposure to cause structural congenital anomalies in humans is very scarce (Bellinger, 1994; Ernhart, 1992; Winder, 1993). This is mainly because very few human studies have been carried out. An increased risk of minor malformations was found in one study (Needleman et al, 1984). In the same study lead levels were not related to major malformations. Two other studies (Ernhart et al, 1986; McMichael et al, 1986) did not find a significant association between prenatal lead exposure and congenital malformations. An advantage of all three studies is that levels of lead were measured in the blood of the mothers, giving relatively accurate exposure estimates. A recent study in the U.K.(Bound et al, 1997) found that mothers in areas with a larger proportion of houses with high lead concentration in drinking water had a higher risk having a baby with a neural tube defect (NTD). More deprived areas had higher proportions of houses with high lead concentrations which may explain some of the above relationship. The relationship between lead and anencephaly was still statistically significant after controlling for the effect of deprivation, relationships for other NTDs and all NTDs combined were not.

Other pregnancy outcomes such as length of gestation and birth weight have been studied more frequently in relation to lead exposure than congenital anomalies, but evidence remains inconsistent for these outcomes since both positive and negative associations have been reported (Andrews et al, 1994; Bellinger, 1994; Ernhart, 1992). In positive reports the risk of growth related outcomes (low birth weight, small for gestational age, intra uterine growth retardation) begins to rise at maternal and cord blood lead levels of approximately 12-15μg/dl, levels not much higher than average levels found in the general population (McMichael et al, 1986). The relationship between blood lead levels and reduced IQ scores in young children is now well established (Goyer, 1996).

Lead has been reported to cause mutations in the male germ cells and may via this route affect the development of the fetus (Barlow and Sullivan, 1982). Increased numbers of chromosomal aberrations have been reported in lead workers, but data is sparse and

findings conflicting (Uzych, 1985; Winder, 1993). Some occupational studies have suggested weak associations between paternal lead exposure and spontaneous abortions (Lindbohm et al, 1991), congenital malformations (Sallmen et al, 1992) and perinatal deaths (Kristenen et al, 1993).

2.3.4.2 Mercury

Mercury is present in the environment as metallic mercury, as inorganic mercury compound, and in organic form. Mercury is used in electrical equipment, dental preparations, paints, fungicides and pesticides, fluorescent lamps, and some batteries (Roeleveld et al, 1990; Wade et al, 1993). The largest input of mercury into the environment is deposition in landfills, followed by industrial emissions into the air (ENDS, 1996). Industrial sources and municipal waste each count for about half of the mercury that is landfilled each year (ENDS, 1996; Hutton and Symon, 1986). The disposal of dental amalgam to sewers is thought to be a major contributor to mercury levels in U.K. surface waters (ENDS, 1996).

The most toxic compound of mercury is methyl mercury. Practically all mercury compounds are teratogenic in animal experiments (Schardein, 1985). The most common malformations produced by methyl mercury in animals are cleft palate, limb defects, and brain and facial malformations (Chang et al, 1980). Metallic mercury vapour and inorganic mercury compounds can cause growth retardation and pre-and postnatal mortality in animals (Barlow and Sullivan, 1982). Little is known about the mutagenicity of mercury, but effects on mitosis, which can cause aneuploidy (numerical chromosome abnormilities), have been described as the most evident mutagenic effects of mercury compounds (Leonard et al, 1983).

Methyl mercury is one of the only environmental chemicals that has been recognised to cause teratological anomalies in humans. Mercury poisoning during pregnancy in residents around the Minamata bay in Japan caused central nervous system anomalies in new-borns (Chang et al, 1980; Koos and Longo, 1976). Brain damage, cerebral palsy and mental retardation were reported in infants born to exposed mothers. Similar effects were reported in Iraq after grain treated with methyl mercury was consumed, and in several case reports after other instances of mercury poisoning.

Effects of inorganic/metallic mercury on reproduction have been examined in women exposed to mercury through work in dentistries and mercury plants, but evidence was not sufficient to assess the effect of exposure during pregnancy (Barlow and Sullivan, 1982). A few more recent studies have looked at the relation between inorganic mercury and reproductive failures but results are inconsistent. Spontaneous abortions and congenital

malformations were significantly related to mercury levels in hair of dentists and dental assistants (Sikorski et al, 1987), but not in women exposed to inorganic mercury vapour in a lamp factory (De Rosis et al, 1985). Numbers of cases of congenital malformations and spontaneous abortions were very small in both studies.

2.3.4.3 Cadmium

Cadmium is used in the manufacturing of batteries, electroplating, pigments, paints, silver solders, plastic stabilisers, alloys, and pesticides (Roeleveld et al, 1990; Wade et al, 1993). Metal-refining plants, municipal incinerators and fossil fuel combustion are important air emission sources of cadmium (Wade et al, 1993). Cadmium is present in cigarette smoke and smokers may have two times the cadmium exposure of non-smokers (Wade et al, 1993).

In all species tested so far cadmium has been shown to be embryo lethal, teratogenic and fetotoxic (Barlow and Sullivan, 1982). Cadmium may cause a wide range of malformations, whereby facial malformations are a consistent and prominent finding(Chang et al, 1980). Teratogenic effects of cadmium are highly dependent on species, strain, administration route and dose. Chromosomal anomalies, such as hyper- and diploidy, have been induced by cadmium in gametes of certain species.

In humans, information about effects of cadmium on pregnancy is very scarce. A few studies have found decreases in birth weight with increase in cadmium levels in hair and placental cadmium (Frery et al, 1993; Huel et al, 1981). Results from these studies are difficult to interpret however, because of the possible interrelationship between cigarette smoke, cadmium, and low birth weight. A review by Jarup et al(1998) reports on two other studies which found cadmium levels in women exposed to occupational or environmental cadmium not to be associated with low birthweight in the offspring. One of these was a study of non-smoking women exposed to cadmium from a nearby smelter(Loiacono et al, 1992). This study found no association between their placental levels of cadmium and low birth weight. Cadmium levels in non-smoking women living near the smelter were similar to levels reported in smokers. Jarup et al(1998) conclude that, although only limited data is available, it is currently unlikely that cadmium in tobacco smoke causes birth weight reductions.

2.3.4.4 Arsenic

Arsenic occurs naturally in the earth's surface (Wade et al, 1993). In the past arsenic has been widely used in herbicides, fungicides, and wood preservatives, and it is still being used

in glass and ceramic production and as a metal alloy. The main industrial sources of arsenic emissions into the atmosphere are metal smelters, coal combustion, and burning of agricultural wastes (Wade et al, 1993). Fossil fuel combustion is the main source of arsenic inputs into landfill in the U.K. (Hutton and Symon, 1986).

A variety of malformations have been induced by arsenic, in particular sodium arsenate, in rats, mice, and hamsters at doses below maternal toxicity (Schardein, 1985). These malformations included exencephaly, eye defects, renal defects, and skeletal defects (Domingo, 1994). Arsenic is mutagenic in some mammalian cell systems and has produced chromosomal damage in human cells (Bhamra and Costa, 1992). Case reports have observed fetal death after maternal arsenic poisoning (Schardein, 1985), but there is very little other information about effects of prenatal arsenic exposure in humans. Nordenson et al (1978) found an increased number of chromosomal aberrations among workers exposed to arsenic in a smelter in Sweden emitting arsenic, lead and other potentially toxic chemicals. Separate studies reported an increase in spontaneous abortions but no increase in congenital malformations and a significant decrease in birth weight around the smelter (Nordstrom et al, 1978; Nordstrom et al, 1979). Apart from parity no other potentially confounding variables (like social class) were taken into account. Zierler et al (1988) studied congenital heart defects in relation to concentrations of a range of chemicals (arsenic, barium, cadmium, chromium, lead, mercury, selenium, silver, fluoride, nitrate and sodium) in the drinking water supplied to the town in which the mother lived. Arsenic was the only chemical related to an increase in heart defects: concentrations of arsenic above the detection limit were related with a 3-fold increase in the risk of coarctation of the aorta.

2.3.4.5 Chromium

Chromium is used in alloys, electroplating, and pigment manufacturing (Wade et al, 1993). Chromium is present in the environment mainly in two oxidation states, hexavalent (Cr VI) and trivalent (Cr III), which differ in physical and chemical properties and toxicity. Cr VI is the most toxic form. Cr VI compounds are more mobile in soil and goundwater than Cr III(Wade et al, 1993). Both forms bind well to small particles in the air.

Chromium VI is genotoxic in experiments (De Flora et al, 1990) and is a well-known human carcinogen (Alcedo and Wetterhahn, 1990). Chromium III on the other hand has not shown such effects (Alcedo and Wetterhahn, 1990). Very little data is available on teratogenic effects of chromium from animal studies and there is to my knowledge no human literature. Domingo et al (1994) review the developmental toxicity of chromium in

experimental animals and report on only two studies which found that malformations were induced after chromium exposure in hamsters but not in mice.

2.3.5 Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) are important environmental pollutants because of their high potential for bioaccumilation. PCBs have been used in wide range of products, including hydraulic fluids, plasticizers, transformers and capacitors, and carbon-less copy paper (Harrad et al, 1994). The production of PCBs has been banned by Western countries since the 1970s. PCBs have a low solubility and strong adsorption to soil particulates which will limit their mobility in landfill sites (Department of the Environment, 1978). Low concentrations can however be found in leachate from landfills. PCBs can be released from landfill sites into the air as trace compound in landfill gas (Harrad et al, 1994) or bound to dust particulates (Hermanson and Hites, 1989). Harrad et al (1994) estimate the emissions of PCBs from landfill to be only a minor contributor to the total U.K. PCB emissions into the atmosphere, an estimate criticised by ENDS (ENDS, 1994) as being to low. Volatilisation of PCBs from soils is reported to be the main emission source (Harrad et al, 1994).

Malformations (oral clefts, exencephaly, hydronephrosis) have been observed in mice and rats after exposure to certain PCBs, but in general PCBs do not appear to induce gross malformations (Barlow and Sullivan, 1982; Schardein, 1985). Low birth weight, peri- and postnatal mortality have consistently been reported below maternal toxicity levels.

PCBs have been reported to be human teratogens (Brent and Beckman, 1990). The first indication that PCBs are teratogenic in man came in the consumption of rice oil contaminated with PCBs, causing the "Yusho" (oil disease) epidemic in Japan. Apart form PCBs other contaminants like furans were found in the rice oil. Among 13 exposed mothers, who all had the Yusho disease, 2 stillbirths were reported and babies were born with skin stains (cola-coloured babies), conjunctivitis and neonatal jaundice (Kuratsune et al, 1972). All live born babies were also below the mean weight for gestational age and 5 were small for gestational age. After poisoning of cooking oil with PCBs in Taiwan similar effects were noted: exposed children were shorter and lighter, and had skin, nail, and teeth anomalies (Rogan et al, 1988). Low birth weight has been reported also after PCB exposure from maternal fish consumption (Fein et al, 1984) and occupational exposure (Taylor et al, 1989). Prenatal exposure to PCBs has been reported to affect cognitive function of children

(Jacobson and Jacobson, 1997). Major structural congenital malformations have not been documented in humans after PCB exposure.

2.3.6 Conclusions

Most of the agents commonly found in landfill site contamination and reviewed in this section have shown teratogenic or mutagenic properties in animal experiments, although a number do not appear to produce gross structural malformations (benzene, toluene, vinyl chloride, lead, PCBs). Evidence from experimental data is difficult to extrapolate to humans because doses are often much higher in experimental settings and because of interspecies variations in susceptibility to chemical exposures.

Of the chemicals reviewed in this section, organic solvents have been most frequently studied in humans. Case reports of solvent abuse suggests that extremely high exposures to toluene may cause congenital malformations. Increased risks of congenital malformation have been reported for certain occupations with likely solvent exposure and for exposure to solvents in drinking water. Results generally lack consistency and rarely assess relationships between specific solvent exposures and specific malformations.

Literature on teratogenic effects in humans of exposure to the other chemical groups reviewed in this section is very scarce. Lead has been linked to functional and intellectual development of children after pre and postnatal lead exposure but there are only a few studies that assess malformation risk. Information on teratogenic effects of mercury and PCB exposures comes almost exclusively from very high dose situations. In these situations mercury has caused damage to the central nervous system and PCBs have reported to cause skin, nail and teeth anomalies and low birth weight. Structural malformations have not been reported after PCB exposure. Information on cadmium, arsenic and chromium exposure is too scarce to draw any conclusions regarding human teratogenicity. Vinyl chloride exposure, occupational or environmental, has not convincingly been linked to congenital malformations in humans, but again studies are few.

2.4 HEALTH EFFECTS OF RESIDENCE NEAR HAZARDOUS WASTE LANDFILL SITES - A REVIEW OF EPIDEMIOLOGICAL LITERATURE

2.4.1 Introduction

This section reviews all major epidemiological studies published since 1980 on health effects related to residence near landfill sites in North America, Europe and elsewhere. The section focuses not just on congenital anomalies but on all adverse health outcomes. Studies on the health effects of landfill sites have mainly been carried out in North America and existing reviews focus entirely on this literature (National Research Council, 1991; Upton, 1989). Recent publications of large studies both in and outside North America warrant an update of evidence presented in previous reviews. Special attention is paid in this section to recent studies and studies outside the U.S. which have not been included in previous reviews.

Throughout this review the term landfill is used for any controlled or uncontrolled disposal of waste to land. Relevant papers were found through computerised literature searches on MEDLINE (Medline database, National Library of Medicine, Bethesda, MD, USA) and BIDS (BIDS databases, Joint Information Systems Committee, University of Bath, U.K.) from 1980 through to 1998, using keywords 'landfill' and 'hazardous waste site'. In addition, papers were traced through references listed in previous reviews. All papers found in this manner which studied health effects in residents near waste landfill sites, and which were published in journals available through the British Library and Libraries of the University of London were included in this review. A few papers referred to in previous reviews could not be traced because they were published in local journals in the U.S. Published reports of recent studies which have not yet appeared in peer-reviewed journals have been included in the review. A few abstracts of European studies have been included although full research papers of these studies have not yet been published, since they importantly reflect growing concerns about landfill in Europe. A total of nearly 50 papers, reports and abstracts were in included in the review.

Investigations of the health risks to those employed in the handling, transport, clean-up, or maintenance of substances at landfill sites are very scarce. They include two health surveys which found high prevalence of symptoms such as respiratory, skin, and neurologic symptoms (Gelberg, 1997, Hertzman, 1987). Health studies of landfill workers have not been included in this review.

Studies measuring exposure to landfill sites by using biological markers of early health effects, such as chromosome damage and liver damage, have been discussed in section 2.2. Evidence for teratogenic potential of chemicals commonly found in contamination from landfills sites has been discussed in section 2.3.

The majority of studies evaluating possible health effects in human populations living near landfill sites investigate communities near one specific waste disposal site ('single-site' studies), frequently in response to concerns from the public about reported contamination from the site, or reported clusters of disease. A small number of studies have addressed the risks of living near waste sites independent of whether the sites caused concern, by a-priori specifying a number of sites for study. These will be referred to as 'multi-site' studies. Single and multi-site studies have different methodological problems and are therefore discussed separately in this section. Studies included in the review are summarised in Table 2.8 (single-site studies) and Table 2.9 (multi-site studies). Discussion of individual single and multi-site studies is preceded by a discussion of issues common to the interpretation of all epidemiological landfill studies.

2.4.2 Issues common to the interpretation of landfill studies

A general problem in epidemiological studies of landfill sites, whether studying single or multiple sites, is that there is insufficient information regarding potential human exposures from landfill sites. Exposure to landfills is by definition difficult to measure (see also section 2.2) and resources are rarely available in epidemiological studies to carry out extensive exposure measurements or modelling. Therefore, epidemiological studies have based the assessment of exposure to landfill mainly on surrogate measures, such as residence in an area close to a waste site, or distance of residence from a waste site. The use of such surrogate, indirect exposure measurements can lead to misclassification of exposure which, if not different for diseased and non-diseased persons, will decrease the sensitivity of the study to find a true effect.

In addition to being hampered by insufficient exposure data, the study of landfill exposures is complicated by the fact that if residential populations are exposed to chemicals from landfill sites, it will generally be to low doses of mixtures of chemicals over long periods of time. Associations with such low-level environmental exposures in the general population are by their nature hard to establish. Low dose exposures are generally expected to generate small

increases in relative risk that will be difficult to distinguish from 'noise' effects introduced by confounding factors and biases.

Some issues related to specific health outcomes should be noted in both single and multi-site studies. A general problem in studies of cancer incidence is the long latency period between exposure and clinical manifestation of the cancer. Studies may not always allow for a long enough latency period which reduces their power to pick up long term effects. Moreover, because of the long latency period, a considerable number of people may have migrated into or out of the exposed areas between time of exposure and time of diagnosis, which will lead to misclassification of exposures. Low birth weight is thought to be relatively sensitive to effects of chemical exposures (Sullivan, 1993). It is also relatively easy to collect accurate information on birth weight from birth certificates. However, a large number of risk factors are associated with low birth weight (including smoking, socio-economic status, nutritional factors, parental height) (Kramer, 1987), and these may act as confounding factors, giving biased estimates of association with residence close to a site. Congenital malformations have fewer established risk factors than other reproductive outcomes such as low birth weight (see further section 2.5), and studies of congenital malformations may therefore be less affected by confounding factors, although unknown risk factors could of course still play a confounding role. Also, congenital malformations represent an aetiologically very heterogeneous set of conditions; analyses of the total malformation rate (all defects combined) have the advantage of larger numbers but may not be sensitive enough to pick up increases in risk of specific defects. The grouping of malformations into groups that are aetiolocigally similar is difficult because of lack of knowledge on causes of specific defects. Grouping therefore always entails a compromise between large enough numbers and aetiological specificity (Khoury et al, 1992).

2.4.3 Single site studies

The investigation of single landfill sites has been important as a response to community concerns; many of the single-site studies discussed below are prompted by public concerns, often under considerable political pressure. This means that they are prone to recall and reporting biases that may weaken the investigations and partly explain increases in reported health outcomes. Single-site studies have sometimes examined a vast range of possible health outcomes, often without a specific disease hypothesis being proposed a-priori. Such 'fishing expeditions' are thought to be of less scientific value than studies that start with a clear hypothesis (Upton, 1989). Including these 'fishing expeditions' in evaluating the

consistency of findings across multiple studies is important nevertheless when assessing evidence for health risks.

A less avoidable problem in single-site studies is that the size of populations living near waste sites is generally small and, especially when the outcome is a rare disease, this can seriously limit the statistical power of an investigation.

Single site studies discussed in this section are grouped into those studying 'hard' end-points such as cancer and reproductive outcomes, those studying self-reported health outcomes and symptoms, those following-up reported clusters of disease near landfill sites with geographical comparisons of disease rates, and those specifically investigating the contamination of well water used for drinking water or other domestic uses in relation to health effects. These last studies were discussed separately to determine whether conclusions can be drawn about specific pathways of exposure.

2.4.3.1 Studies of cancers and reproductive outcomes

Large quantities of toxic materials (residues from pesticide production) were dumped at the landfill of Love Canal, New York State, during the 1930s and 40s, followed by the building of houses and a school on and around the landfill in the 1950s. By 1977 the site was leaking and chemicals were detected in neighbourhood creeks, sewers, soil, and indoor air of houses. This led to one of the most widely known and publicised incidents of environmental pollution from landfill. Exposure of Love Canal residents, although not well-understood, may have occurred via inhalation of volatile chemicals in home air or via direct contact with soil or surface water (Paigen et al, 1987). The drinking water supply was not contaminated. Chemicals detected at Love Canal were primarily organic solvents, chlorinated hydrocarbons and acids, including benzene, vinyl chloride, PCBs, dioxin, toluene, trichloroethylene, and tetrachloroethylene. Several studies were carried out to detect whether Love Canal residents suffered adverse health effects.

Janerich et al (1981) compared cancer incidence for the Love Canal area with data for the entire state from 1955-77 and found no increase in cancer rates at Love Canal for any organ site. These included leukaemia, lymphoma, and liver cancer which were thought to be the cancers most likely to result from exposures to the chemicals found at the site. A limitation of the study is that no information was available on confounding factors such as socio-economic status and smoking.

Infants and children have been the subject of other Love-Canal studies. A cross-sectional study (Paigen et al, 1985) reported an increased prevalence of seizures, learning

problems, hyperactivity, eye irritation, skin rashes, abdominal pain, and incontinence in children living close to the Love Canal site compared to controls from other areas, as reported by the parents of the children. It has been noted in previous reviews(British Medical Association, 1991; Upton, 1989) that this study was carried out in 1980, two years after the residents of Love Canal had become aware of the hazardous waste problem, when media and public interest were high and people were being evacuated. This makes it likely that the results were biased by differential reporting of health problems. However, a similar population of children (spending 75% or more of their childhood in the Love Canal area) had a significantly shorter stature for their age than control children after allowing for factors such as birth weight, socio-economic status, and parental height(Paigen et al, 1987). Vianna and Polan (1984) found an excess of low birth weight (less than 2500g) during the period of active dumping (1940-53) in areas of Love Canal where exposure had been highest. Rates of low birth weight between 1960-78 after the site had been closed were comparable to upstate New York as a whole. It is not clear whether exposure from Love Canal was highest during the active dumping period, or during the period after the site was closed, when the building of houses near the site increased and the landfill was leaking. A study by Goldman et al (Goldman et al, 1985) reported a three-fold risk of low birth weight for children exposed during gestational life to the Love Canal area compared to that for control children born elsewhere, in a period covering 1965-1978. Data were analysed separately for homeowners and renters so that groups of similar socio-economic status were compared, and after allowing for confounding factors the risk of low birth weight was significantly increased for homeowners only. This finding is difficult to interpret because there are no strong reasons to believe that homeowners would be more susceptible than renters to the effect of toxic chemicals. In the same study an increased risk of birth defects was observed for both homeowners and renters. Information on birth defects relied mainly on reports from parents. Some recall bias can therefore be suspected, in particular for defects of lesser severity, but this is unlikely to account for the entire association found for major birth defects.

Love Canal, NY. Janerich 1981	Geographical comparison	Love Canal census tract; comparison: New York State	Residence in Love Canal census tract	Cancer: liver, lymphomas, leukaemia, other organ sites.	No increased incidence
Love Canal, NY. Paigen 1985	Cross-sectional	523 Love Canal children; 440 control children	Proximity to site, at least 5 months residence in Love Canal area	Self-reported health problems: seizures, learning problems, hyperactivity, eye irritation, skin rashes abdominal pain, and incontinence	Increased prevalence of all symptoms
Love Canal, NY. Paigen 1987	Cross-sectional	428 Love Canal children, 493 control children	Born in Love Canal and more than 75% of life in Love Canal	Children's stature, weight, weight for stature	Shorter stature for Love Canal children. No difference in weight
Love Canal, NY. Vianna and Polan 1984	Retrospective follow-up	174 births near site; 443 live births in rest of Love Canal area; all births in New York State	Residence in Love Canal area	Low birth weight (LBW)	Higher percentage of LBW in exposed area; excess in period of active dumping.
Love Canal, NY. Goldman 1985	Retrospective follow-up	239 exposed children, 707 unexposed controls	Residence in Love Canal area during pregnancy	LBW, birth defects	Three-fold risk of LBW (homeowners only); increased risk for birth defects (homeowners and renters).
Lipari Landfill, NJ. Berry and Bove 1997	Retrospective follow-up	2,092 births in proximate area; 6,840 births in control area	Residence at birth in area closest to landfill	Average birth weight, LBW, preterm birth.	Significantly lower average birth weight, higher proportion of LBW and prematurity during the time of heaviest pollution.
BKK Landfill, CA. Kharazzi 1997	Retrospective follow-up	25,216 births	Residence in census tract, proximate zone, and frequency of odour complaints.	LBW, fetal mortality, infant mortality, prematurity	No difference over entire study period; moderate decrease in birth weight in high odour complaint zone in period of highest exposure.
Miron Quarry, Quebec. Goldberg 1995	Case-control	7,977 LBW cases and 7,856 control births	Residence in areas adjacent to landfill and level of estimated exposure to biogas	LBW, very-LBW, preterm birth, small for gestational age	Excess in LBW and small for gestational age births, no excess in very-LBW or preterm birth.
Miron Quarry, Quebec. Goldberg 1995	Geographical comparison	Residents of Montreal Island	Residence in areas adjacent to landfill and level of estimated exposure to biogas	Cancers of 17 organ sites for men and 20 organ sites for women.	Increase in incidence of stomach, liver, lung and prostate cancer for men, stomach and cervix-uteri cancer for women.
Drake, Clinton County, PA. Budnick 1984	Geographical comparison	cancer deaths and birth defects compared to Pennsylvania and US.	Residence in Clinton and 3 other counties surrounding waste site	Bladder cancer and cancers of other organ sites; birth defects.	Increase in bladder cancer deaths in Clinton, increase in number of other cancers in Clinton and 3 surrounding counties. No excess in birth defects.
Drake, Clinton County, PA. Logue 1986	Cross-sectional	179 long-term exposed residents, 151 residents in comparison areas	Residence in area near waste site	14 self-reported diseases, 15 self-reported symptoms	Increased prevalence of skin problems and sleepiness
Lowell, MA. Ozonoff 1987	Cross-sectional	1049 exposed, 948 unexposed residents	Residence in household close to site	36 self-reported health problems	Increased prevalence of minor respiratory symptoms (wheezing, cough, persistent cold), irregular heart beat, fatigue, bowel complaints

continued

[illegible]	follow-up	comparison households	edge of site; long/short-term residence		symptoms, skin and respiratory disorders, eye problems, muscle weakness
Stringfellow site, CA. Baker 1988	Cross-sectional	403 exposed households, 203 comparison households	Residence in proximate area	19 self-reported diseases, 23 symptoms; mortality, cancer incidence, low birthweight, birth defects, spontaneous abortion	Increase in majority of self-reported diseases and symptoms. No significant association for mortality, cancer morbidity, reproductive effects
Queensland, Australia. Dunne 1990	Cross-sectional	257 residents in exposed zones, 105 in comparison area	Distance based zones: zone 1: <300m and zone 2: 300-	Self-reported diseases and symptoms, miscarriages, stress levels	Increased reporting of majority of symptoms, miscarriages, stress
McColl waste site, CA. Lipscomb 1992	Follow-up survey	57 high, 66 low, 70 unexposed residents	Exposure zones based on odour zones	22 self-reported health problems	Two-fold increase in 64% of reported symptoms
Houston, Texas. Dayal 1995	Cross-sectional	321 high exposed persons, 351 persons with low/minimal exposure	Cumulative exposure index based on distance from sites and amount of chemicals present at sites	29 self-reported health problems	Excess in reporting of 11 of 29 symptoms: mainly neurologic symptoms
Harris County, Texas. Miller 1997	Cross-sectional	456 exposed residents, 481 comparison persons	Residence near site	14 self-reported health problems	Increased reporting of 11 of 14 symptoms.
Montchanin, France. Zmirou 1994	Retrospective follow-up	694 residents	Individual exposure index based on concentration of pollutants and daily activity of study subjects.	Amount of prescribed medication for selection of diseases (respiratory, ophthalmological, dermatological, gastrointestinal, neurological)	No relationship between individual exposure index and drug consumption.
Montchanin, France. Deloraine 1995	Case-control	432 cases and 384 controls	Individual exposure index based on concentration of pollutants and daily activity of study subjects	Dermatological, respiratory, eye gastrointestinal diseases, psychological disorders and other conditions	Relationship between exposure level and existing cases of respiratory and psychological conditions.
North-Rhine Westfalia, Germany. Greiser 1991	Geographical comparison	3 counties adjacent to waste dump compared to whole region	Communities near dump, distance of community to dump	Leukaemia, multiple myeloma, malignant lymphoma	Excess in leukaemia incidence
Walsall, England. Muir 1990	Geographical comparison	Ward surrounding landfill compared to whole region	Residence in landfill ward, surrounding wards, area down-wind from landfill	All childhood cancers	No excess of childhood cancer
Nant-y-Gwyd, Wales. Fielder 1997	Geographical comparison	5 wards near landfill compared to 22 wards elsewhere	Wards near landfill	Mortality rates, hospital admissions for asthma, cancer, and other conditions, spontaneous abortions, birth defects, drug prescriptions	No consistent differences in mortality rates, hospital admissions, spontaneous abortions. Excess in birth defects before and after start of the landfill. Increase in prescriptions for certain medications.
Illinois. Mallin 1990	Geographical comparison	Cancer rates in 8 counties in Illinois compared to national rates	Residence in town with contaminated wells	Bladder cancer	Excess in bladder cancer in town with contaminated wells

continued

Cutler 1988	comparison	national rates			
Woburn, MA. Lagakos 1986	case-control	20 leukaemia cases, 164 control children	Exposure index based on fraction of water supply from contaminated wells	Childhood leukaemia	Significant association with exposure index
	Retrospective follow-up	4,396 pregnancies and 5,018 children under 18	Exposure index based on fraction of water supply from contaminated wells	Childhood disorders; adverse pregnancy outcomes: spontaneous abortions, perinatal death, LBW, birth defects	Increase in congenital eye/ear anomalies, CNS/ chromosomal/ cleft anomalies; perinatal deaths; kidney/urinary tract disorders, lung/respiratory disorders
Woburn, MA. Byers 1988	Cross-sectional	28 family members of Woburn leukaemia cases, 30 healthy controls	Being a family member of a Woburn leukaemia case	Immunological abnormalities, medical examination	Immunological abnormalities in family members
Santa Clara County, CA., Swan 1989	Retrospective follow-up	Births in exposed census tracts compared unexposed	Residence in census tract served by contaminated water supply	Congenital heart defects	2-fold excess in cardiac anomalies
Santa Clara County. Deane 1989	Retrospective follow-up	Pregnancies in exposed census tract; pregnancies in unexposed census tract	Residence in census tract served by contaminated water supply	Spontaneous abortions, birth defects, LBW	Increase in spontaneous abortions and birth defects; no excess in LBW
Santa Clara County. Wrensch 1990	Retrospective follow-up	Pregnancies in 2 exposed census tracts; pregnancies in 2 unexposed census tracts	Residence in 2 census tracts served by contaminated water supply	Spontaneous abortions, birth defects, LBW	No excess in spontaneous abortions or malformations in new exposed study area
Santa Clara County. Wrensch 1990	Retrospective follow-up	Pregnancies in 2 exposed census tracts	% water in census tract from contaminated well, estimated concentration of solvents	Spontaneous abortions, birth defects	No relation between abortion or malformation rate and estimated exposure
Santa Clara County. Shaw 1990	Case-control	145 cases with cardiac malformations, 176 non-malformed births	Mother's consumption of home tap water	Congenital heart defects	Elevated risk for consumption of more than 4 glasses of tap water compared to none.
Santa Clara County. Deane 1992	Retrospective follow-up	349 pregnancies in 1 exposed and 1 unexposed census tract	Mother's consumption of home tap water	Spontaneous abortions, birth defects	Spontaneous abortions: significant trend with number of glasses tap water per day. Birth defects: no trend
Santa Clara County. Wrensch 1992	Retrospective follow-up	1,016 pregnancies in exposed and unexposed areas	Mother's consumption of home tap water	Spontaneous abortions, birth defects, LBW	Spontaneous abortions: 7-fold risk for any versus no tap water. Birth defects: non-significant increase. No association with LBW
New Jersey. Najem 1994	Cross-sectional	676 exposed residents, 778 unexposed	Residence in high exposure area based on groundwater flow	Self-reported disease: cancer, liver disease, respiratory illness, skin disease, seizures	Statistically significant increase in respiratory disease and seizures (not significant after accounting for smoking)
Dauphin County, Logue 1985	Cross-sectional	65 exposed residents, 66 residents from control households	Residence in households with contaminated well-water	15 self-reported health symptoms and 14 self-reported diseases	Increased reporting of eye irritation, diarrhoea, sleepiness.

Berry and Bove (1996) studied birth weight at the Lipari Landfill in New Jersey, a site for municipal and industrial waste. Leachate from the site migrated into nearby streams and a lake adjacent to a residential area. Inhalation of volatile chemicals emitted from the landfill and contaminated waters was thought to be the most important exposure pathway. The site closed in 1971 after complaints of residents, but the heaviest pollution was estimated to have occurred during the late 1960s to the mid-1970s. The study found a convincing increase in proportion of low birthweight babies (<2500 g) and a lower average birth weight in the population living closest (within a radius of 1 km) to the landfill in the time period when potential for exposure was thought to be greatest (1971-1975), compared to a control population. Although information on some confounding variables such as smoking, alcohol consumption, and socio-economic status was not available, mothers in the exposed area were more highly educated and therefore appeared to be of higher socio-economic status. One would expect a higher birth weight in areas of higher socio-economic status, so as the authors point out, confounding by socio-economic status does not explain the lower birth weight found. In time periods before and after heavy dumping and off-site pollution birth weights were higher in the area closer to the site than in the control area which supports the hypothesis that pollution from the waste site may have been related to low birth weight in the community close to the site.

A range of reproductive effects including low birth weight was studied around the large BKK hazardous waste disposal site in Los Angeles County, California (Kharrazi et al, 1997), after previous investigations of vital records found that trends in low birth weight and neonatal deaths corresponded closely with times and quantities of dumping at the landfill. Results for the whole study period showed no increase in adverse reproductive effects, but during the period of heaviest dumping birth weights were significantly lower in exposed areas than control areas, using odour complaint frequency zones to classify exposure. All results were adjusted for education, income, and race. The decrease in mean birth weight found in the high odour complaint zone was small (59 grams) compared to that found in the Lipari Landfill study (192 grams) and was less than a third of birth weight reductions caused by smoking during pregnancy (Berry and Bove, 1996). Odour complaint frequency zones corresponded better with vinyl chloride monitoring data and meteorology around the site than did census tract areas or distance based (<0.7 miles) exposure zones, and this was therefore thought to be the most accurate method for classifying exposure. Using census tract or distance based exposure zones smaller decreases in mean birth weight were found (35.2 grams, $p=0.02$ and 20.4 grams, $p=0.25$ respectively).

Miron Quarry, a large (the third largest in North-America) municipal solid waste site in Montreal, Quebec has prompted studies on both reproductive outcomes (low birth weight and pre-term births) (Goldberg et al, 1995) and cancers (Goldberg et al, 1995). Gas from the site was the main environmental and health concern and a range of volatile organic compounds (VOCs), including a number of recognised or suspected human carcinogens, had been detected in the gas. An excess of 20% in low birth weight was found among babies of mothers who were living in the high exposure area adjacent to the landfill at the time of delivery, taking account of confounding factors such as education and age of the mother. No excess was found in the low exposure zone compared to a control area. Exposure zones were based on proximity to the site and accounted for the direction of dominant winds. Control areas were selected to be similar to exposure areas on a number of sociodemographic variables so as to limit the potential for confounding. The cancer study used the same exposure zones and control areas and found an increase in the incidence of cancers of the stomach, liver, prostate, and lung for men, and stomach and cervix/uterus for women. Incidences of cancers of other organ sites were not increased in the exposed areas. Age and sex were the only confounders that could be controlled for directly and the authors admit that area matching for sociodemographic factors was based on fairly broad zones. The landfill started operation in 1968 and cancer incidence was studied between 1981 and 1988, which allowed a maximum latency of only 20 years among those residents in the area throughout the period.

At the Drake Superfund Site, an industrial chemical dump, in Pennsylvania, widespread on and off-site contamination of groundwater, soil and surface water with organic (benzene, chlorinated benzene, phthalates) and inorganic (arsenic, mercury) compounds, prompted a cancer mortality and birth defects study (Budnick et al, 1984) and a community health survey (Logue and Fox, 1986). Air monitoring near the site identified a small number of organic compounds but the main exposure route was thought to be direct contact with surface waters and soil in recreational areas near the site. Budnick et al (1984) found an increase in mortality from bladder cancer (cancer of primary a-priori concern because of aromatic amines detected on and off-site) in the male population of one of the counties surrounding the waste site compared to average mortality rates in the entire state and the U.S. Bladder cancer in females did not show such an effect. The authors point out that an occupational effect (for males working in the Drake chemical plant) may explain the fact that the association was found in men only. No excess in risk of birth defects was found. The subsequent health survey (Logue and Fox, 1986) found increased reporting of sleepiness and skin problems in the exposed community and concluded that it was difficult to say whether toxic chemicals

from the site, overreporting of symptoms by the exposed community (reporting bias), or other factors such as stress and occupational exposure, caused these symptoms.

2.4.3.2. Studies of self-reported health symptoms

A number of other community health surveys have investigated a wide range of health problems, including respiratory symptoms, irritation of skin, nose and eyes, gastro-intestinal problems, fatigue, headaches, psychological disorders, and allergies. These studies have been carried out in response to concerns from the public, often triggered by smells and odours from the sites. In a number of studies self-reported health problems were increased in exposed populations (people living closed to the waste sites) compared to control populations (Drake Superfund Site (Logue and Fox, 1986); Lowell, Massachusetts (Ozonoff et al, 1987); Hamilton, Ontario (Hertzman et al, 1987); Stringfellow, California (Baker et al, 1988); Queensland, Australia (Dunne et al, 1990); McColl waste site, California (Lipscomb et al, 1991); Houston, Texas (Dayal et al, 1995); Harris County, Texas (Miller and McGeehin, 1997); see Table 2.6 for details). The majority of these health surveys rely on residents reporting symptoms and diseases through questionnaires or interviews. The possibility exists that higher reporting rates of symptoms in exposed areas are at least partly explained by reporting and/or recall biases. Importantly from a public health point of view, the findings of high symptom reporting, whether or not due to differential self-reporting, may indicate the impact that stress and concerns related to landfill can have on ill-health and/or perceived ill-health. In the survey by Ozonoff et al (1987) residents who indicated they were 'worried' about neighbourhood pollution reported more symptoms than those who were not 'worried' both in the exposed and the control area. Although this does not eliminate the possibility of an effect of toxic chemicals from the site, it suggests that stress and/or recall bias may have been responsible for the findings. Miller and McGeehin (1997) and Dunne et al (1990) found increased symptom prevalence only in residents who indicated they were worried about, or aware of, an environmental problem in their neighbourhood. The study by Lipscomb et al (1991) showed a two-fold risk in most symptoms for residents who were worried compared to those who were not worried among the exposed population and the authors concluded that being worried rather than a toxicological effect from the site explained the symptoms. Hertzman (1987) used medical records to confirm certain symptoms and found no over- or underreporting. They concluded that this finding indicated limited reporting bias; however, only a small proportion of the respondents' records were reviewed. Moreover, seeing a physician (and therefore having a medical record) may itself be related to concerns about the site. Baker et al (1988) studied self-reported health problems as well as mortality, cancer

incidence, and pregnancy outcomes from medical registers at the Stringfellow waste dump in California. Self-reported diseases and symptoms were the only outcomes that differed between exposed and unexposed areas. Again a higher 'perception of threat' was related to a higher risk of nearly all self-reported symptoms.

The complicated relation between worry, odour perception, and symptom reporting related to hazardous waste landfill sites is further discussed by several authors (Neutra et al, 1991; Roth et al, 1985; Shusterman et al, 1991).

Two recent studies around the French landfill of Montchanin used records of prescribed medication (Zmirou et al, 1994) and cases from GP practices (Deloraine et al, 1995) to define health outcome, in order to avoid biases related to self-reporting of symptoms. Exposure classification in both studies was based on an individual index taking into account the concentration of airborne pollutants and daily activities of study subjects. High concentrations of VOCs were detected in areas near the site and both leachates and air from site were reported to be highly toxic in 1988 and 1989, shortly after site closure. Consumption of drugs prescribed for most conditions from 1987 to 1989 did not show a trend with exposure level although a slight trend was found for drugs taken for ear, nose and throat and pulmonary conditions. In the second study patients with conditions thought to be associated with dump emissions were compared to other GP patients and an association was found for respiratory symptoms and psychological disorders. Again, consulting a doctor for such conditions and subsequent diagnosis of the conditions by the physician, may be related to fears of adverse effects from the landfill, rather than toxic chemical effects.

2.4.3.3 Cluster investigations

In addition to the above papers a number of reports are available of geographical comparison studies initiated after high rates - clusters - of specific diseases were reported in the vicinity of landfill sites. For example, increased rates of leukaemia found in communities nearest to a toxic waste dump in North-Rhine Westfalia, Germany, supported a GP report of a cluster near the site (Greiser et al, 1991). A cluster of childhood cancer reported by residents near a landfill site in Walsall, England was not confirmed in a geographical comparison of rates in the ward containing the site to expected rates based on the regional average (Muir et al, 1990). Only short reports of these two investigations have been published. Concerns from residents and a GP about increased rates of congenital abnormalities (specifically gastroschisis, a defect in the abdominal body wall) near the Welsh landfill of Nant-y-Gwyddon were supported by the finding that rates of congenital abnormalities in exposed

wards were almost 1.9-fold those in unexposed wards over the period of 1990-1996 (Fielder et al, 1998). However, rates in the exposed wards were already high (1.9 fold those of unexposed wards) between 1983 and 1987 before the site opened, and it is unlikely therefore that these increased rates were due to the landfill. Four cases of confirmed gastroschisis indicated a significant 9-fold excess in exposed wards between 1989 and 1996. A cluster of bladder cancer cases in one town in Illinois, U.S., was observed by researchers and subsequently linked to the presence of two contaminated wells close to a landfill site (Mallin, 1990).

A general problem in the interpretation of all cluster investigations, is that localised areas of high disease density may occur even as part of a random pattern of disease. It is difficult to distinguish clusters derived from this random pattern from those where there is a common underlying local cause (Alexander and Cuzick, 1992; Rothman, 1990). Also, areas with higher disease densities, although part of the random pattern of disease, may be selectively picked for study.

2.4.3.4. Studies of drinking water contamination incidents

The presence of chemicals in groundwater and drinking water is an important factor in determining the risk posed by landfill sites. However, it does not tell us what effect, if any, the consumption of contaminated water has on human health. Studies of adverse health effects prompted by the contamination of well water used for drinking water and other domestic uses by hazardous substances from waste disposal sites (mainly sites where chemical waste drums were buried), are discussed below. Literature on contaminated water and potential health effects is more extensive than that presented in this section, which focuses only on water contamination directly related to the disposal of waste. The 1991 review by the National Research Council gives a more comprehensive review of studies on contamination of domestic water supplies and health effects and concludes that although the available literature is "scanty and not conclusive", drinking water contamination could lead to adverse health effects (National Research Council, 1991). Most of the studies summarised below have been discussed extensively in previous reviews (National Research Council, 1991; Upton, 1989).

In Woburn, Massachusetts, toxic chemicals (industrial solvents, mainly trichloroethylene) from a waste disposal site were detected in municipal drinking water wells. Residents of Woburn reported a cluster of 12 leukaemia cases in children and a first study confirmed that this number was significantly higher than expected on the basis of national rates (Cutler et al,

1986). The problems with cluster analyses are discussed above. Because of lack of information on exposure to the contaminated wells it was not possible in this first report to link the leukaemia cases with exposure to the well-water. Lagakos et al (1986) followed up these findings by compiling an exposure score for residential zones in Woburn, using information on what fraction of the water supply in each zone had come from the contaminated wells annually since the start of the wells. Childhood leukaemia incidence, perinatal deaths, congenital anomalies and childhood disorders were studied in relation to the exposure scores. A significant excess was found again comparing leukaemia rates for Woburn with national rates and an association was found between leukaemia incidence and exposure scores. The pregnancy outcome survey found associations with eye/ear congenital anomalies and central nervous system/oral cleft/chromosomal anomalies (mostly Downs syndrome), but not with low birth weight or most childhood disorders. Pregnancy outcomes were self-reported in this study but because residents were not aware of their exact exposure score the authors conclude that it is unlikely that this led to substantial differential overreporting. Byers et al (1988) undertook a study of 28 family members of patients with leukaemia in Woburn. Damage to the immune and nervous systems was found in exposed relatives but not in unexposed controls. Exposure in this study was not measured by exposure to contaminated well-water but by being related to a leukaemia patient in Woburn, which makes it difficult to interpret the findings. The authors point out that it is impossible to say whether the association is due to an inherited predisposition or to a common environmental exposure of family members to agents that damage the immune system.

A number of studies followed the contamination of two drinking water wells in Santa Clara County, California, with chlorinated solvents that had leaked from an underground waste storage tank. Residents living near one of the contaminated wells reported a cluster of adverse pregnancy outcomes, mainly spontaneous abortions and congenital heart defects. A first investigation (Swan et al, 1989) confirmed a significant excess of cardiac anomalies in the service area of the water company that operated the contaminated well compared to an unexposed area. The excess was found within the potentially exposed time period and not in an unexposed time period after the well was closed. The authors conclude that the solvent leak was an unlikely explanation for the excess of cardiac anomalies found because the excess occurred mainly in the first 12 months of the exposed time period, and there was a significant ($p=0.03$) deficit of cases during the second 8 months corresponding to the time when exposure was thought to be more certain. However, it is unclear when the leak started and the potentially exposed period was defined beforehand as the full 20 months' period. A second study in the same area reported an increased risk of all congenital malformations combined and spontaneous abortions (Deane et al, 1989). A follow-up study including a

second exposed area did not observe an increase in either outcome in this second area, even though it was thought to have the same water exposure as the original area (Wrensch et al, 1990). An exposure study estimating monthly concentrations of solvents in each census tract, found no difference in probability of exposure between women with adverse pregnancy outcomes and women with normal births (Wrensch et al, 1990). Subsequent studies investigating water consumption in Santa-Clara County report significant associations between reported tap water consumption and risk of cardiac defects (Shaw et al, 1990) and spontaneous abortions (Deane et al, 1992; Wrensch et al, 1992), regardless of whether women lived in areas that received contaminated water. As the authors of these studies point out, recall biases cannot be excluded.

Leakage from an industrial dump of chemical waste drums in New Jersey caused contamination of groundwater and well-water with organic chemicals (including benzene, toluene, trichloroethylene) and lead. Najem et al (1994) found higher self-reported prevalence of respiratory disease and seizures but not cancer, liver illness, and skin disease in people living in a high exposure area estimated on the basis of ground water flow patterns. Residents in the high exposure area more often used private drinking water wells, ate home grown food, and smoked than unexposed populations. When these factors were adjusted for, differences in health outcomes disappeared. Adjusting for possible exposure routes such as local food consumption and use of private wells may have led to overadjustment however, which would explain why no differences in health outcome were found.

An ex-military base in Dauphin County, Pennsylvania containing drums of toxic chemicals, fly ash and other waste; well water for homes located on the perimeter of the site was contaminated with trichloroethylene, PCBs, pesticides and other chemicals (Logue et al, 1985). Residents were instructed to stop using the water. Higher rates of eye irritation, diarrhoea, and sleepiness were reported by residents of households with contaminated well-water than by residents of households not having contaminated water.

2.4.4 Multi-site studies

The problems with single-site studies prompted by community pressures have increasingly been recognised and recently several large studies have investigated adverse health effects near sets of hundreds of sites selected independently of community concerns or reported disease clusters (Table 2.9). These studies have the additional advantage of large numbers of subjects which would give them enough statistical power to detect small increases in risk

of rare disease such as birth defects and specific cancers. On the other hand, their large scale makes exposure assessment even more complicated than in single-site studies, as adequate information must be collected for each of many sites. A number of the studies discussed below have used the U.S. National Priority Listing (NPL) of hazardous waste sites developed by the U.S. Environmental Protection Agency for the selection of their sites. The NPL ranks all hazardous waste sites in the U.S. deemed to be of considerable threat to the environment or public health. NPL sites have been relatively well assessed with respect to the potential or actual migration of hazardous chemical substances from the sites through ground water, surface water, and air (National Research Council, 1991), see also section 2.2. Most multi-site studies however, were not able to distinguish between different types and pathways of contamination and, in absence of better exposure data, based their assessment of exposure on distance of residence from the sites or residence in an area with a site. Exposure misclassification, if non-differential, may be expected to dilute true effects in these investigations. Multi-site studies have mainly investigated cancers and reproductive outcomes.

2.4.4.1 Cancer studies

Griffith et al (1989) identified 593 NPL sites over the entire U.S. where contamination of groundwater used for drinking water had been detected by laboratory analyses. Cancer mortality rates for counties containing one or more of these NPL sites were compared to those for counties not containing sites and raised levels of lung, bladder, stomach, and rectum cancer were found. These results were not adjusted for confounding factors such as socio-economic status and smoking, and are therefore difficult to interpret.

A case-control study in New-York State examined lung-cancer in relation to residence in a census tract with a waste site (Polednak and Janerich, 1989). Twelve waste sites known to contain suspected lung carcinogens were studied. A questionnaire survey amongst next-of-kins of the deceased cases and controls attempted to collect information on factors such as smoking, diet, education and residential history. Smoking was significantly more frequent amongst cases, but there was no association between having lived in or duration of living in an exposed census tract and risk of lung cancer. Low response rates (around 60%) and possible recall bias limit this study.

A recent study in New York State investigated cancer risks near 38 landfills where migration of landfill gas through soil was likely (Lewis-Michl et al, 1998). Migration of soil gas could

result in indoor exposure in nearby houses to hazardous VOCs carried with the landfill gas. Potential exposure areas were defined around each site, and extend 250 feet from the landfill at 36 sites, and 500 feet at two sites. Incident cases of cancer collected from the New York State Cancer Registry were compared with a random selection of deaths from causes other than cancer, matched by age and sex. Only cancers of the liver, lung, bladder, kidney, and brain, and non-Hodgkin lymphoma and leukemia, were studied as they were regarded potentially sensitive to chemical exposures. Statistically significant excesses in the defined exposure areas were reported only for bladder cancer in women and leukemia in women. The results were adjusted for sociodemographic characteristics of the areas of residence. No information was available on individual factors such as smoking, nor on how long cases and controls had been living at certain addresses. The use of deceased controls makes interpretation of this study extremely complicated. The deceased population from which controls were selected may differ from the population from which the cases were drawn on a number of variables including their location of residence.

2.4.4.2 Studies of reproductive outcomes

Shaw et al (1992) carried out a study on the risk of congenital malformations and low birth weight in areas with landfills, chemical dump sites, industrial sites, and hazardous treatment and storage facilities in the San Francisco Bay area, California. Census tracts were classified as *a)* no hazardous site in area, *b)* hazardous site in area but no evidence of human exposure, and *c)* hazardous site and plume in the area with evidence of potential human exposure. A small increase (1.5-fold) in risk was found for heart and circulatory malformations in the areas with potential human exposure. This increased risk was present across chemical classes and exposure routes. Risk of other malformations or low birth weight was not significantly increased. Results were adjusted for some potential risk factors (maternal age, race, sex of child, birth order) but not for socio-economic status.

Sosniak et al (1994) investigated the risk of adverse pregnancy outcomes for people living within 1 mile of a total of 1281 NPL sites over the entire U.S. The risk for low birth weight and other pregnancy outcomes (infant and fetal death, prematurity, and congenital anomaly) was not associated with living near a site after taking into account a large number of potential confounding factors, including socio-economic variables, collected through questionnaires. However, only around 63% of women originally sampled for the study returned the questionnaire and were included in the study. Also, it is unclear how congenital anomalies were defined and no subgroups of malformations were studied.

Table 2.9: Multi-site studies

Reference	*Study Design*	*Study Sties*	*Study Subjects*	*Exposure Measure*	*Health Outcomes Studied*	*Reported Findings*
Griffith 1989	Geographical comparison	593 NPL waste sites in US	339 counties with waste site, more than 3,000 without	County with site	Cancer mortality	Increased rates of cancer of the lung, bladder, stomach, and rectum
Polednak 1989	Case-control	12 sites in New York State	339 deceased lung-cancer cases, 676 deceased controls	Residence in census tract with site, duration of residence	Lung cancer	No association
Lewis-Michl 1998	Case-control	38 sites with likely landfill gas migration in New York State	9,020 cancer cases, 9,169 deceased controls	Residence within 250 feet of a site	Cancer of liver, lung, bladder, kidney and brain; non-Hodgkin lymphoma, leukemia.	Excess of female bladder cancer and female leukemia
Shaw 1992	Case-control	300 sites in 1,072 census tracts in California	5,046 birth defects cases and 28,085 control births. 190,4000 births for birthweight analysis	Residence in census tract with site and potential for human exposure	Birth defects, LBW	1.5-fold increased in risk of heart defects. Other malformations and birth weight not associated.
Sosniak 1994	Case-control	1281 NPL sites in US	17,407 births	Residence within 1 mile	Birth weight, birth defects, foetal deaths, infant deaths	No association between adverse pregnancy outcomes and living near a NPL site.
Geschwind 1992	Case-control	590 waste sites in New York State	9,313 live births with birth defects and 17,802 normal control births	Residence within 1 mile and hazard score of site	Birth defects	Increased risk for all malformations (12%), integument system, nervous system, musculoskeletal. Indications for dose response relation with exposure risk
Marshall 1995	Case-control	643 waste sites in New York State	473 cases with central nervous system defects; 3,305 musculo-skeletal cases; 12,436 control births	Ratings of exposure probability within 1 mile of each site.	Birth defects of central nervous system and musculoskeletal defects	No association between two types of defects and proximity to waste sites.
Hall 1996	Case-control	317 waste sites in New York State	259 cases of end-stage renal disease and 259 controls	Residence within 1 mile, exposure probability, years of residence within 1 mile	End-stage renal disease	Non-statistically significant increase in risk of renal disease for ever living within 1 mile, having lived within 1 mile for more than 12 years, and a medium/high probability of exposure
Croen 1997	Case-control	105 NPL and 659 non-NPL sites in California	507 NTD cases and 517 controls; 210 heart defects, 439 oral clefts, and 455 controls.	Census tracts: no site, non-NPL site, NPL site. residence within 1 and within 1/4 mile from site	Birth defects: NTD, heart defects and oral clefts	No increased risks relating to residence in census tract with site. Small, non-significant increase in risk of NTD and heart defects for living within 1/4 mile.

Abbreviations: LBW, low birthweight; NTD, neural tube defects; NPL, national Priority List sites

Geschwind et al (1992) investigated the risk of congenital malformations in the vicinity of 590 hazardous waste sites in New York State. A 12% increase in congenital malformations was found for people living within 1 mile of a site. For malformations of the nervous system, musculo-skeletal system, and integument (skin, hair, and nails), higher risks were found. Some associations between specific malformation types and types of waste were evaluated, and found to be significant. A dose-response relationship (higher risks with higher exposure) was reported between estimated hazard potential of the site and risk of malformation, adding support to a possible causal relationship. However, a follow-up study of Geschwind's findings found no relation between two selected types of malformations (central nervous system and musculo-skeletal) and living near a hazardous waste disposal site (Marshall et al, 1997). The study did report an increased risk of central nervous system defects for those living near solvent or metal emitting industrial facilities. Subjects for the first two years of this study were also included in Geschwind's study, and two more years were studied. Marshall et al (1997) attempted to improve the exposure measurement in the first study by assessing the probability of specific contaminant-pathway combinations in 25 sectors of the 1 mile exposure zones (Marshall et al, 1993). The risk of particular pathways or contaminant groups could not be investigated, however, because of limited numbers of cases in each subgroup. Hall et al (1996) used the same method of exposure assessment to study renal disease near 317 waste sites in 20 counties in New York State. Increased risks were found for associations between renal disease and residential proximity to a site (within 1 mile), the number of years lived near a site, and a medium or high probability of exposure, although the associations did not reach statistical significance.

A study by Croen et al (1997) based exposure measurement on both residence in a census tract containing a waste site and on distance of residence from a site. Three specific types of birth defects: neural tube defects, heart defects, and oral clefts were studied. Little or no increase in the risk was found using either measure of exposure. Risk of neural tube (2-fold) and heart defects (4-fold) were increased for maternal residence within 1/4 mile of a site although numbers of cases and controls were too small (between 2 and 8) for these risk estimates to reach statistical significance. Births were ascertained from non-military base hospitals only and the authors point out that the increased risk of NTD may have resulted from lower ascertainment of exposed controls than exposed cases where exposure zones included military bases. Military-base residents with NTD-affected pregnancies may have been more likely to deliver in non-military hospitals than military-base residents with unaffected pregnancies.

2.4.5 Conclusions

The presence of large quantities of mixtures of potentially hazardous chemicals in landfill sites close to residential populations has increasingly caused concern. Concerns have led to a substantial number of studies on the health effects associated with landfill sites. From this review it can be concluded that increases in risk of adverse health effects have been reported near individual landfill sites and in some multi-site studies. Although biases and confounding factors cannot be excluded as explanation for these findings, these may indicate real risks associated with residence near certain landfill sites. Lack of direct exposure measurement and resulting misclassification of exposure affects most landfill site studies and can limit their power to detect health risks.

It is possible that studies not showing associations have been less likely to be included in this review, because they may have been less likely to be submitted or selected for publication, thereby causing the review to be biased towards studies that did report positive associations. However, a number of so-called 'negative' studies have been published and included in this review. I feel that most large, good-quality, epidemiological investigations, particularly those starting with an a-priori hypothesis rather than a specific cluster, would have resulted in publications, whether or not the findings were positive.

An increase in self-reported health outcomes and symptoms, such as headaches, sleepiness, respiratory symptoms, psychological conditions, gastro-intestinal problems, has been found consistently in health surveys around sites where local concerns were evident (Baker et al, 1988; Dayal et al, 1995; Dunne et al, 1990; Hertzman et al, 1987; Lipscomb et al, 1991; Logue and Fox, 1986; Logue et al, 1985; Miller and McGeehin, 1997; Najem et al, 1994; Ozonoff et al, 1987; Paigen et al, 1985). In these health surveys symptoms were usually reported by the exposed population without further confirmation of the diagnoses by medical examination. It is not possible at this stage to conclude whether the symptoms are an effect of direct toxicological action of chemicals present in waste sites, and/or an effect of stress and fears related to the waste site, and/or an effect of reporting bias - the tendency of exposed people to remember and report a more symptoms than unexposed people. Several authors have discussed the possibility that odour complaints and related worry about a site may trigger symptoms of stress-related disease or lead to an increased awareness of existing symptoms (Neutra et al, 1991; Shusterman et al, 1991). Further research in this area is urgently needed to improve our understanding of the impact of social factors and risk

perceptions on both actual and perceived ill-health in waste site communities. Issues of environmental equity and environmental justice must form an integral part of such research.

Evidence for a causal relationship between landfill exposures and cancers is still extremely weak. Cancers are difficult to study because of long latency periods as was discussed in previous studies. Also, cancer studies have mainly compared incidence or mortality rates between geographical areas without collecting adequate information on confounding factors. Excesses in bladder, lung, and stomach cancer and leukaemia were reported in more than one study (Budnick et al, 1984; Goldberg et al, 1995; Griffith et al, 1989; Lagakos et al, 1986; Lewis-Michl et al, 1998; Mallin, 1990). Well-designed studies with long follow-up and good quality information about confounding factors such as smoking, are needed to confirm these findings.

A number of studies have suggested a relationship between residential proximity to landfill sites and adverse pregnancy outcomes. An increase in infants with low birth weight has been the most consistent finding in single-site studies (Berry and Bove, 1996; Goldberg et al, 1995; Goldman et al, 1985; Kharrazi et al, 1997; Vianna and Polan, 1984). Small increases in the risk of birth defects and certain specific birth defects (cardiac defects, central nervous system defects, musculo-skeletal defects) have been reported, mainly in multi-site studies (Croen et al, 1997; Geschwind et al, 1992; Goldman et al, 1985; Shaw et al, 1992). Studies are too few and results too inconsistent however to draw conclusions regarding possible causality of these relationships. Fetuses, infants, and children are generally thought to be more vulnerable and therefore experience toxic effects at lower doses than the adult population (British Medical Association, 1991). The finding of shorter stature in Love Canal children (Paigen et al, 1987) may also be an example of this.

Abnormalities in liver function (see section 2.2 (Clark et al, 1982)) and renal disease (Hall et al, 1996) have also been reported in relation to hazardous waste exposure, although in single studies only.

For the future planning and regulation of landfill sites it is important to know which types of sites are most likely to entail risks. As discussed in section 2.1 landfill sites may differ enormously in the conditions that render them 'hazardous', and conditions that determine the exposure to and resulting health risks posed by any waste site are likely to be unique to that particular site. I have not in this review attempted to relate technical aspects of waste disposal to health effects. Much of the existing epidemiological work investigates large, old sites, uncontrolled dumps and sites where heavy off-site migration of chemicals was

detected. On the basis of current evidence, we cannot extrapolate findings for these individual sites to landfill sites in general, or conclude which landfill sites are more likely than others to affect the health of nearby human populations.

It is also not possible to determine whether sites with airborne or waterborne exposures are more likely to pose a risk to human health. Although drinking water contamination is usually the primary concern related to landfill sites, in most cases local water supplies do not originate from the local area. The majority of studies therefore concern landfill sites where no local drinking water wells were present and potential exposure was either airborne or through other routes such as direct contact and consumption of home grown vegetables.

At present, information regarding adverse health effects of exposure to landfill sites in European countries is largely lacking.

2.5 RISK FACTORS FOR CONGENITAL MALFORMATIONS : LIFE-STYLE AND SOCIODEMOGRAPHIC FACTORS

The aim of this section is to review risk factors in the parental environment other than exposures to environmental chemicals reviewed in section 2.3, in order to assess their role as potential confounding factors in the current study, and to provide general background to this thesis.

The most important potential confounder in the relationship between residence near landfill sites and risk of congenital anomaly is socio-economic status. This section reviews the literature on socio-economic variation in the risk of congenital anomaly is reviewed in detail. The role of other demographic and life-style risk factors is discussed more briefly, based on information from existing review articles where possible.

2.5.1 Socio-economic status

Studies of environmental risk factors such as occupation or smoking in relation to congenital anomalies often include analyses of socio-economic variables in order to assess potential for confounding although results are not always explicitly presented. I considered it beyond the scope of this thesis to review this very extensive body of literature. This section is therefore limited to studies specifically investigating the relationship between socio-economic status and risk of congenital anomaly. Whereas socio-economic status has been established as a risk factor for a range of adverse perinatal and infant outcomes such as low birth weight (Leon, 1991; Reading et al, 1993) and perinatal, neonatal, and postneonatal mortality (McIntosh Gray, 1982; Office for National Statistics, 1996), surprisingly little literature exists specifically examining socio-economic status as a risk factor for congenital anomalies. Knowledge about socio-economic variation in the risk of congenital anomalies is important however, not only to assess the potential for socio-economic confounding in this study and other epidemiological studies, but in more general because the presence or absence of socio-economic inequalities, and the extent of such inequalities, can be an important aetiological clue, as it has been for discovering the nutritional aetiology of neural tube defects (Little and Elwood, 1992). Moreover, the analysis of socio-economic inequalities in risk of congenital anomaly can provide information to underpin needs assessment, service targeting and evaluation of population interventions such as the periconceptional folic acid supplementation campaign (Health Education Authority, 1998).

Studies of all congenital anomalies combined have reported either no clear socio-economic inequalities (Ericson et al, 1984; Stone and Womersley, 1989; Tuohy et al, 1993) or a higher prevalence among lower social classes (Knox and Lancashire, 1991; Olsen and Frische, 1993) (Table 2.10). The studies that report socio-economic inequalities report relative risks of 1.3 (Knox and Lancashire, 1991) and 1.6 (Olsen and Frische, 1993) for the most deprived versus the most affluent social class as measured by occupation of the father.

Table 2.10: Studies of socio-economic variation in the risk of all congenital malformations combined.

Reference	*Social class measure*	*Results*
Ericson et al., 1984; Sweden	income, occupation, nationality, etc	RR 1.09 (95% CI 0.97-1.23) for class III (low social class) vs. I (high)
Stone and Womersley, 1989 (abstract); UK	neighboorhood type	no correlation
Knox and Lancashire, 1991; UK	occupation father	1.3 fold increase in class V (low) vs. I (high)
Tuohy et al., 1993; New Zealand	education and salary	no trend
Olsen and Frische, 1993; Denmark	occupation father	OR 1.6 (95% CI: 1.0-2.4) for unemployed vs. class 1 (high social class)

Few studies have examined the presence or absence of socio-economic inequalities in specific congenital defects, with the exception of neural tube defects for which a strong increase in risk among lower social classes has been well documented (Little and Elwood, 1992). Differences of 2 to 4 fold between social classes have been documented up to the mid-70s (Little and Elwood, 1992). There has been little recent study except a Californian study which found an excess risk of neural tube defects in women from more deprived neighbourhoods in the period 1989-1991 (Wasserman et al, 1998).

For Down Syndrome both higher (Knox and Lancashire, 1991) and lower (Lopez et al, 1995; Stone and Womersley, 1989) prevalences among lower social classes or residents of more deprived areas have been reported, probably mainly secondary to differences in maternal age distribution between the social classes (Lopez et al, 1995). Lopez et al (1995) found that controlling for maternal age weakened but did not completely annul the trend of increasing risk with increasing social class. Knox and Lancashire (1991) and Stone and Womersley (1989) did not control their results for maternal age differences between social classes.

A number of studies have shown trends of higher risk in lower social classes for oral clefts, which seems to be related to cleft palate in particular (Knox and Lancashire, 1991; Olshan et al, 1991; Womersley and Stone, 1987, Hemminki et al, 1980). Up to 3-fold increases in risk

in the lowest compared to the highest social classes have been reported for cleft palate. Inconsistent results have been reported for cleft lip (with or without cleft palate), showing both increasing risks with lower social class (Olshan et al, 1991) and no clear socio-economic variation (Ericson et al, 1984; Knox and Lancashire, 1991; Womersley and Stone, 1987).

There are inconsistent reports concerning the existence of social class inequalities for hypospadias. Knox and Lancashire (1991) report no socio-economic variation, Olshan et al (1991) an increasing risk with decreasing social class. Higher prevalences for lower social classes have been reported, by single studies, for congenital cataract, some cardiovascular anomalies, selected genitourinary anomalies, polydactyly, syndactyly, limb reduction defects and hydrocephalus (Correa-Villasenor et al, 1991; Hemminki et al, 1980; Knox and Lancashire, 1991; Olshan et al, 1991). Knox and Lancashire (1991) report an absence of social class variation for omphalocele/exomphalos, tracheo-oesophageal fistula, anal atresia, diaphragmetic hernia, and ocular deformities and a higher risk with higher social class for congenital dislocation of the hip. Gastroschisis has been reported to be associated with low social class (Hemminki et al, 1982; Torfs et al, 1994). Dolk et al (1998) report no socio-economic variation in the prevalence of anophthalmia.

Many risk factors could mediate the impact of socio-economic status on the prevalence of congenital anomalies including nutritional factors, life-style, environmental and occupational exposures, access to and use of health services, parity and maternal age, and ethnic origin. Some risk factors discussed in subsequent sections, such as ethnicity, maternal age, and parity, may also be associated with congenital anomaly risk independently of socio-economic status.

2.5.2 Maternal age

For chromosomal anomalies, especially trisomies, a strong trend of increasing risk with increasing maternal age has been well documented. Maternal age is the single most important risk factor for Down syndrome (Gaulden, 1992) with maternal age specific Down syndrome prevalence increasing from 1:1500 for 15-29 years, to 1:800 for 30-34 years, and 1: 270 for 35 to 39 years.

Studies on maternal age patterns in non-chromosomal anomalies report inconsistent findings, particularly with regard to specific malformation groups. For all malformations

combined U and J-curves with high risks in young mothers and old mothers, have been most commonly documented (Croen and Shaw, 1995). Croen and Shaw (1995) in a large population based study report the risk for all non-chromosomal malformations to be lowest for mothers between 25 and 29, and highest amongst young mothers (< 20 years) and older mothers (>35): a typical U-curve. Only live births were studied, however, and differences between maternal age groups in uptake of prenatal screening and subsequent terminations of pregnancy may explain some of the findings. The U-curve pattern reported in this study was similar for first and second-born infants, but differed between ethnic groups with blacks showing no differences in congenital anomaly prevalence with maternal age and all other ethnic groups (white, hispanic, other) showing a U-curve.

Specific anomalies showing the highest risk amongst younger mothers in the study by Croen and Shaw (1995) were central nervous system defects and abdominal wall defects. The increase risk in abdominal wall defects amongst younger mothers is likely to be due to the increased prevalence of gastroschisis in young maternal age groups, a well documented finding (Calzolari et al, 1993; Haddow, 1993; Torfs et al, 1990). Increases in risks of gastroschisis of up to 7-fold for mothers under 20 years compared to mothers of 25 years and older have been reported (Haddow, 1993). Gastroschisis has been reported to be associated with low social class (previous section), smoking and cocaine use after controlling for maternal age (Torfs et al, 1994).

Knox and Lancashire (1991) report U and J curves for most malformation groups with the exception of exomphalos, renal agenesis, cleft palate, syndactyly, limb reductions, eye malformations, and diaphragmatic hernia for which there was no relationship with maternal age. Baird et al (1991) find no maternal age differences in the prevalence of most malformation groups apart from patent ductus arteriosus and pyloric stenosis, showing a decrease in risk with increasing maternal age.

Knox and Lancashire (1991) also report a maternal age effect for congenital heart defects, independent of parity, with a 2-fold increase or mothers aged 40 or more compared to mothers aged 24 or less. This finding may be due to chromosomal heart defects being included in the group of congenital heart defects. It is not clear whether or not chromosomal anomalies were excluded. Other authors report no association between maternal age and major heart defects (Baird et al, 1991; Croen and Shaw, 1995).

For neural tube defects reports on maternal age effects are inconsistent and have been described as "confusing" (Elwood and Little, 1992). U-curves, negative linear trends (decreasing risk with maternal age), positive linear trends, and absence of an association have all been documented (Elwood and Little, 1992). U-curves have most commonly been reported but often effects of parity were shown to be at least partly responsible for this effect.

Elwood and Little conclude that independent maternal age effects are small. High risks of neural tube defects have been reported to be related to first births and parity of 3 or more (Elwood and Little, 1992).

The prevalence of other congenital anomalies has also been reported to vary with parity (number of previous live and stillbirths), with primiparous mothers generally showing higher risk than mothers of multiple parity (Hemminki et al, 1982). The effects of parity and maternal age are strongly interrelated and difficult to separate.

Paternal age has rarely been studied as a risk factor for congenital anomaly. A paternal age effect could be of interest as indication for a role of germ cell mutation (Elwood and Little, 1992). Some previous studies have shown increased in paternal age to be associated with increases in new dominant single gene mutations (McIntosh et al, 1995). Patterns of increasing risk with increasing paternal age have been reported after maternal age adjustments, mainly in single studies, for cataract, limb reduction defects, ventricular septal effects, atrial septal defects, chondodystrophy, and neural tube defects (Lian et al, 1986; McIntosh et al, 1995; Savitz et al, 1991). Elwood and Little (1992) report no association between prevalence of neural tube defects and paternal age after controlling for maternal age. Young fathers have been reported to have higher risks of neural tube defects, hypospadias, cystic kidney, heart defects and Down syndrome (McIntosh et al, 1995; Zhan et al, 1991). McIntosh (1995) reported the relative risk for Down syndrome to be higher (RR=3.8) in young fathers (<20 years) than in older fathers (35+ years) compared to the 25-29 age comparison group. Other studies have reported no association between paternal age and risk of Down syndrome (Lian et al, 1986; Savitz et al, 1991).

2.5.3 Ethnicity

The prevalence of congenital anomalies varies between ethnic groups. Differences in the incidence of congenital malformations or in mortality from malformations have been documented in the U.K. (Balarajan and McDowall, 1985; Balarajan and Raleigh, 1989; Knox and Lancashire, 1991; Leck and Lancashire, 1995; Terry et al, 1985), and elsewhere (Chavez et al, 1989; Polednak, 1986). Hypotheses to explain these differences include socio-economic variations, dietary factors, genetic factors, consanguinity, and maternal age (Polednak, 1986; Young, 1987). In the U.K. the highest malformation rates have been reported for South Asians (India, Pakistan, Bangladesh), particularly for Pakistanis (Balarajan and McDowall, 1985; Balarajan and Raleigh, 1989; Knox and Lancashire, 1991; Terry et al, 1985). This pattern occurred independent of social class in studies that adjust for

social class (Balarajan and Raleigh, 1989). Consanguinity in South Asian couples may partly explain raised malformation rates (Bundey et al, 1991). Terry et al (1985) found consanguinity common in Pakistani but not in Indian couples and concluded that consanguinity could not explain the high malformation rates found in Indians. High risks in South Asian ethnic groups are reported for a range of specific major malformations including anencephalus, anomalies of circulatory system, and limb defects (Balarajan and Raleigh, 1989). A high prevalence of chromosomal anomalies amongst Pakistanis was reported in Birmingham (Terry et al, 1985), but mortality from chromosomal anomalies amongst Pakistani mothers for the whole of England and Wales did not show an excess (Balarajan and Raleigh, 1989).

Afro-Caribbean populations in the U.K. and the U.S. have commonly shown low rates of major congenital malformations, as well as low infant mortality from congenital malformations, compared to whites U.K. (Balarajan and McDowall, 1985; Balarajan and Raleigh, 1989; Chavez et al, 1989; Knox and Lancashire, 1991; Polednak, 1986; Terry et al, 1985). This has been shown to be the case for a range of defects including neural tube defects (Knox and Lancashire, 1991, Balarajan, 1989 #110), specific heart defects (Correa-Villasenor et al, 1991), oral clefts (Knox and Lancashire, 1991), and hypospadias (Knox and Lancashire, 1991). Minor anomalies, particularly polydactyly, are more common in Afro-Caribbean/black than in Caucasian/white populations (Chavez et al, 1989; Knox and Lancashire, 1991; Leck and Lancashire, 1995; Young, 1987).

2.5.4 Life-style risk factors : smoking, alcohol

A range of exposures related to personal habits and life-style factors have been suspected as risk factors for congenital anomalies. These include caffeine, tea, alcohol, cigarette smoke, and illegal drugs (including marijuana, heroin, cocaine) (Kalter and Warkany, 1983). Congenital malformations have not convincingly been associated with caffeine or use of most recreational drugs although the latter are extremely difficult to study (Brent and Beckman, 1990; Kalter and Warkany, 1983). Cocaine has been related to neurological defects and urinary tract malformations in some reports (Brent and Beckman, 1990). Effects of solvent (mainly toluene) sniffing are discussed in section 2.3.2.

Maternal smoking has generally been reported not to be associated with all congenital anomalies combined (Werler, 1997). Werler (1997) in a review of the literature on smoking concludes that data on central nervous system defects and cardiac malformations suggests

that smoking is not a major risk factor for these two groups of congenital anomalies. Maternal smoking has been related to small increases in risk of gastroschisis after adjustment for maternal age and socio-economic status (Haddow, 1993; Torfs et al, 1994; Werler, 1997). Oral clefts have been the most widely studied malformations in relation to cigarette smoking. Studies have shown inconsistent results both for cleft lip and cleft palate but report more frequently positive than absent relationships (Werler, 1997). Risks for smokers compared to non-smokers reported for cleft palate vary between 1.5 and 2.7, for cleft lip from 1.4 to 2.8 (Werler, 1997). Recent reports suggest that the interaction between a genetic factor and maternal smoking leads to an increased risk of oral clefts (Shaw et al, 1996). The relationship between Down syndrome and maternal smoking has been investigated in a number of studies with inconsistent results (Chen et al, 1999; Werler, 1997). A protective effect of smoking found in some of these studies has been suggested to be due to smoking leading to decreased intra-uterine survival of gametes or fetuses with chromosomal anomalies (Hook and Regal, 1991). This theory is controversial and the protective effect of smoking reported is according to others entirely due to residual maternal age confounding (Chen et al, 1999). Most studies report no association between Down syndrome and maternal smoking after maternal age adjustment (Chen et al, 1999; Werler, 1997).

Heavy alcohol consumption can cause a distinct pattern of congenital anomalies, the fetal alcohol syndrome (Jones, 1988). The syndrome is reported only in children of chronically alcoholic women who drank heavily during pregnancy, most to women drinking 8-10 or more units per day (Jones, 1988). There is some discussion about how much alcohol intake constitutes a 'safe' level. Brent and Beckman (1990) report that alcohol is unlikely to constitute a risk for the unborn child when the mother drinks less than two units a day. Others have reported however that small reductions in birth weight may occur at this level (Jones, 1988).

2.5.5 Nutritional and medical risk factors

Nutritional factors suspected of playing a role in the aetiology of congenital anomalies include deficiencies of vitamins A and E, folic acid, zinc, iodine, and amino acids, as well as excess intake of vitamins A and D (Kalter and Warkany, 1983). The role of folic acid deficiency in the aetiology of neural tube defects has led to campaigns to promote the intake of periconceptional intake of folate supplementation (Health Education Authority, 1998) and in some countries to the fortification of foods (cereals, flower) with folic acid.

Supplementation of vitamin A and high intake of liver or liver products in pregnancy is discouraged because of the strong teratogenic properties of excess vitamin A (Dolk et al, 1999). Khoury (1989) reports that birth defects occurred in 25 per cent of fetuses exposed to isotretinoin, a vitamin A congener used as treatment for skin conditions. Isoretinoin can cause a range of malformations including microtia, cardiac defects, and central nervous system defects (Jones, 1988).

Maternal diseases and conditions related to an increased risk of congenital anomaly include phenyl ketonuria, diabetes, hyperthermia, and a number of maternal infections: rubella, cytomegalovirus, herpes simplex, parvovirus B19, varicella zoster, and toxoplasmosis (Brent and Beckman, 1990; Kalter and Warkany, 1983). Kalter and Warkany (1983) estimate about 2 percent of all congenital malformations to be due to infections, 1.4 per cent to diabetes, and up to 1 per cent to other diseases and conditions. They estimate that in total about 3.5 per cent of congenital anomalies is caused by maternal disease.

A number of medical drugs have been recognised as teratogens. These fall under the following main groups: hormone preparations (androgens, progestogens, diethylstilbestrol), antibiotics (tetracycline), anticoagulants (warfarin), anticonvulsants (trimethadione, phenytoins, valproic acid), tranquilizers (thalidomide, benzodiazepine), antineoplastic drugs (cyclophosphamide), and retinoic acid (Vit A, isotretinoin) (Brent and Beckman, 1990; Janerich and Polednak, 1983; Khoury, 1989; Moore and Persaud, 1993). Medical drugs are used commonly by pregnant women: studies in several countries have reported that 70% or more of women take at least one drug during pregnancy (de Jong et al, 1990). Many drugs may have not or insufficiently been tested for teratogenic effects (Kalter and Warkany, 1983; Pasker-de Jong, 1993).

Exposure to high doses of ionising radiation during pregnancy can cause structural congenital malformations in humans (Brent, 1999). The most common malformation reported after high dose radiation exposure is microcephaly. Malformations are reported in offspring of women exposed to doses of over 100 rad during pregnancy, usually from radiation treatment. Exposure to diagnostic radiation has generally not been associated with adverse pregnancy outcomes (Brent, 1999).

CHAPTER 3

METHODS

The first part of this chapter (sections 3.1, 3.2 and 3.3) describes the general study design and methods for data collection of the EUROHAZCON study, a multi-centre European study of risk of congenital malformation in the vicinity of hazardous waste landfill sites. The general design of the EUROHAZCON project is that of a case-control study, comparing cases of congenital anomaly and control births for their proximity to landfill sites. Subsequent sections describe the methodology used to classify malformation subgroups (section 3.4), to measure socio-economic status (section 3.5), to assess exposure, including the scoring of landfill sites according to their hazard potential (section 3.6), and to analyse collected data statistically (3.7).

Funding for the EUROHAZCON project was obtained from the European Commission BIOMED programme, which funded the co-ordination of the project but had no funds available for extra data collection or for individual participants. Therefore, collection of data on exposure, outcome, and potential confounding factors, was limited to routinely registered and easily obtainable information. Methods for data collection were dictated also by the need to ensure standardised data collection in different participating countries throughout Europe.

3.1 EUROHAZCON PARTICIPATING CENTRES

Ten centres in six European countries participated in the EUROHAZCON project (Table 3.1). All centres are population based registries of congenital malformations, with the exception of North Thames (West) which covers all hospitals in that particular region. Centres were selected on the basis of the high quality of their congenital anomaly data and the presence of hazardous waste landfill sites the regions they cover. Six centres are part of the EUROCAT network of regional registers for the surveillance of congenital anomalies in Europe. EUROCAT registers report cases of congenital anomaly to a centrally co-ordinated database following common principles of case ascertainment and a common coding system (EUROCAT Working Group, 1997). Most of the centres participating in EUROHAZCON are regional registers, with the exception of two which have nation-wide coverage but of Down

Syndrome only (England & Wales and Slovenia). Other centres register a wide range of congenital anomalies. North East Italy uses a limited list of 31 anomalies for inclusion. In each centre, the ascertainment of congenital anomalies is based on the use of multiple sources of information such as birth and death certificates, maternity and hospital records, cytogenetic and pathology service reports, and maternal and child health service reports. All centres apart from Slovenia register live births, stillbirths and terminations of pregnancy, and ascertain cases diagnosed at least up to one year of age. Slovenia registers live births and stillbirths only.

Table 3.1: Congenital anomaly registers participating in the EUROHAZCON project

Participating register	*Country*	*Years covered*	*approx. annual number of births covered*
Funen County EUROCAT Register	Denmark	1980-present	5,000
North Thames (West) Congenital Malformation Register (EUROCAT)	United Kingdom	1990-present	47,000
France Central East Registry of Congenital Malformation (Lyon)	France	1978-present	100,000
Antwerp EUROCAT Register	Belgium	1990-present	10,000
Tuscany EUROCAT Register	Italy	1980-present	25,000
Northern Region Congenital Abnormality Survey	United Kingdom	1986-present	40,000
Glasgow EUROCAT Register	United Kingdom	1980-present	13,000
Slovenia Down Syndrome Register	Slovenia	1987-present	21,000
England & Wales Down Syndrome (cytogenetic) Register	United Kingdom	1989-present	600,000
North-East Italy EUROCAT Register	Italy	1989-present	50,000

3.2 SELECTION OF HAZARDOUS WASTE LANDFILL SITES

3.2.1 Definition of study sites

Definition of hazardous waste

The EUROHAZCON study was set up to investigate *hazardous* waste landfill sites, meaning those designated for the disposal of wastes classified as 'hazardous'. It is extremely difficult to define hazardous waste as discussed in section 2.1. Since EUROHAZCON is a European project it was decided to use the definition in the European Directive on Hazardous Waste for the selection of study sites (European Communities Council, 1991). In three annexes this Directive lists categories or generic types of waste (Annex IA and IB), constituents of waste (Annex II), and properties of waste which render them hazardous (Annex III). These three annexes are attached in Appendix 3 of this thesis. Annex IA waste is designated 'hazardous'

unless shown not to have Annex III properties. Annex IB waste which contains any Annex II constituents is designated 'hazardous' unless not possessing Annex III properties. Listed constituents include heavy metals and heavy metal compounds, phenols, cyanides, PCBs, organic solvents, pesticides, and polychlorinated dibenzo furans and dioxins. Waste of domestic origin is specifically excluded from the Directive.

Municipal landfill sites

Emissions from landfill sites not taking hazardous waste, including municipal landfills, may be just as hazardous as designated hazardous waste sites, as was discussed in section 2.1. The types of waste that enter a site may only to a small degree determine the composition of leachate and gaseous emissions. Moreover, municipal waste may contain 'hazardous' substances, although probably not in the same concentrations as 'hazardous' waste. It was decided at a EUROHAZCON participants meeting that municipal sites would not be included in the study in order not to dilute the main subject of the study, and because widening the study to municipal landfill sites would not be feasible within the time scale of the project.

Asbestos and clinical waste

For the purpose of this study, landfill sites are not included if the only hazardous waste they contain is asbestos or hospital and clinical waste. Asbestos wastes and clinical wastes are included in the EC's Hazardous Waste Directive, but although asbestos is a well-known carcinogen it has not been associated with effects on embryonic or fetal development. Hospital and clinical wastes may contain teratogenic and mutagenic chemicals and/or organisms, but designated clinical waste sites are distinctly different from other waste sites in their management and location (often at hospital sites).

Time of operation of the landfill site

It was decided on the advice of local landfill specialists collaborating with the participating centres, that closed landfill sites would be included in the study. The local specialists agreed that contamination hazards associated with landfill sites may remain for at least 50-100 years. Also, it was decided *not* to include sites which had been in operation for less than 5 years at the start of the study period. It was thought that at least 5 years of operation would be needed before a site would pose any substantial hazard to the surrounding environment. Although some off-site contamination may be expected as a results of the actual dumping of the waste (through windblown dust and particles), decomposition processes within a site require a certain quantity and age of waste to generate significant quantities of leachate and landfill gas (section 2.1.2).

In summary, landfill sites eligible for inclusion in the study were those:

- located within the area covered by a participating congenital malformation registry, or a geographically defined part of this area;
- presently in operation or closed;
- having operated for at least 5 years at any time before the start of the study period (see section 3.3.2); and
- containing hazardous waste of non-domestic origin, as defined in the EC Directive on Hazardous Waste (with the exception of asbestos and hospital waste).

Not all participating centres had the resources to cover all hazardous waste landfill sites in their region. Therefore, in some centres sub-regions for selection of sites were identified. In the Northern Region the number of hazardous waste landfills sites was very large (>50) and it was decided to cover only two Counties within this region (Durham and Tyne and Wear). Similarly, one sub-region was specified in France Central East and data collection for the England & Wales Down Syndrome Register was limited to the Merseyside and Essex regions. Other centres covered their entire region.

3.2.2 Questionnaire for characterisation of landfill sites

Questionnaires were developed for the initial characterisation and clarification of eligibility of landfill sites in the participating regions. Appendix 4 includes this Questionnaire for the Characterisation of Landfill Sites. Local landfill specialists collaborated with the participating centres to complete the questionnaires.

The EC directive is fairly recent (1991) and many European countries had not yet incorporated the hazardous waste definition into their laws at the time of this study. At the time sites were selected for the EUROHAZCON project, many participating countries still defined hazardous waste according to their existing laws or had no existing hazardous waste classification. U.K. law for example included definitions of 'controlled waste', 'special waste', and 'difficult waste', which may all include hazardous wastes as defined by the EC Directive. In practice it was therefore not always obvious which sites would fall under the EC definition of hazardous waste, particularly where detailed information on types of waste deposited at sites was not available. In countries that had a legal definition or classification closely matching the EC definition of 'hazardous', this legal definition was used for the initial selection of sites. In the U.K. sites taking 'special waste' most closely matched the EC definition, as did 'Class B' landfill sites in Italy, and 'category 1' landfill sites in France. In all other countries such definitions or classifications could not be used and study sites were

selected from all landfills in a region on the basis of questionnaire information on types of waste deposited.

A total of 28 sites were selected in the 10 participating centres (Table 3.2). Two of these sites, in North-East Italy, were excluded from all later analyses because there were very few cases (2) in the study areas containing these sites. In one region a landfill site identified as 'hazardous' was not included in the study because there was no population nearby (North Thames (West)).

Table 3.2: Study areas, study sites, and study periods

participating centre	*study area*	*study site*	*study period*
Funen County (Denmark)	1	1	1987-93
	2	2	1986-93
North Thames (West) (UK)	3	3	1990-93
	4	4	1990-93
Lyon (France)	5	5	1990-94
Antwerp (Belgium)	6	6	1990-93
	7	7a, b, c	1990-93
	8	8	1992-93
Tuscany (Italy)	9	9	1982-93
	10	10	1982-93
	11	11	1987-93
Northern Region (UK)	12	12	1989-93
	13	13a, b, c, d	1986-93
	14	14	1990-93
Glasgow (UK)	15	15a, b	1990-91
Slovenia	16	16	1989-93
	17	17	1988-93
England&Wales Down	18	18	1989-92
Syndrome Register	19	19	1989-92
	20	20	1989-93
North East Italy*	21	21	1992-93
	22	22	1992-93

*not included in analyses

3.3 DEFINITION AND SELECTION OF CASES AND CONTROLS

3.3.1 Study areas

Around each selected landfill site a study area had to be defined within which cases and controls were to be selected. This area had to be sufficiently large to contain the extent of

any suspected exposure from the landfill site, as well as a large enough unexposed population. The study area could not be too large on the other hand, because of the workload involved in locating cases and controls. In addition, larger areas in general are more likely to contain other factors which may be related to a risk excess or deficit, unconnected to the site, for example socio-demographic factors or other potential sources of exposure such as industrial sites. The choice of the size of the study area was complicated by the lack of information on how far from a landfill site possible contamination can be expected (see also section 2.2).

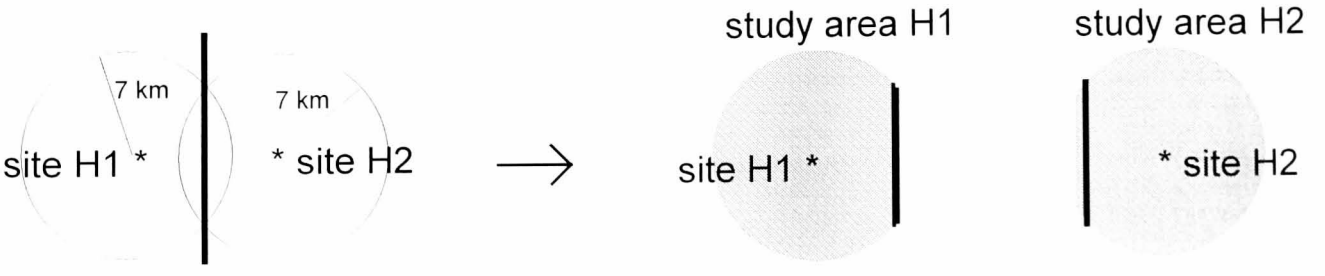
A pilot study was carried out to underpin the study design of the main EUROHAZCON study. For this pilot a small number of cases of congenital anomaly and non-malformed control births were randomly selected in 10 km study areas around one landfill site in each study region. Results of the pilot showed that 50% of cases and controls lived within 5-10 km from the waste sites. Landfill experts advising the study agreed that a distance of 3 km should include any possible exposure and a 3 km zone around each landfill was defined as the zone of 'most likely exposure' (see also section 3.6.1). In the light of the 3 km 'exposure' zone, the 10 km study area chosen for the pilot study included an unnecessarily large (3-10 km) unexposed area, and the study area size for the main study was decided at 7 km.

For sites close to a registry boundary, the study concerned only the part of the 7 km zone that fell within the registry area. Thus areas outside the registry area were treated similarly to unpopulated areas (sea, lake, etc.).

In several regions the 7 km study areas of two or more study sites overlapped. The following method was used for defining overlapping study areas :

i) Where two or more sites were located within 14 km but more than 7 km from each other, the areas of most likely exposure were clearly spatially separated and the study areas around each site could be considered separately. The areas of overlap were split in such a way that all population was allocated to the nearest site, as shown in Figure 3.1. Areas 3 and 4, 9 and 10, 12 and 13, 13 and 14, 18 and 19 were split in this way

Figure 3.1: Study areas for sites that are less than 14 km but more than 7 km apart:



ii) Where two or more sites were within 7 km of each other, large parts of the 3 km zones of 'most likely exposure' were contained within the area of overlap, and it would be problematic to separate effects that the two or more sites may have in this area of overlap. Therefore the 7 km areas around the 2 or more sites were combined into one large area, as shown in Figure 3.2. Sites 15a and 15b were located 6 km from each other so this method *ii)* was used to define study area 15. In study area 13 four sites were located within 7 km of each other: sites 13b and 13c were 2.4 km apart, 13a and 13d 3.3 km, and 13c and 13d 6.9 km. Figure 3.3 shows how method *ii)* was applied in this study area.

Figure 3.2: Study areas for sites that are less than 7 km apart

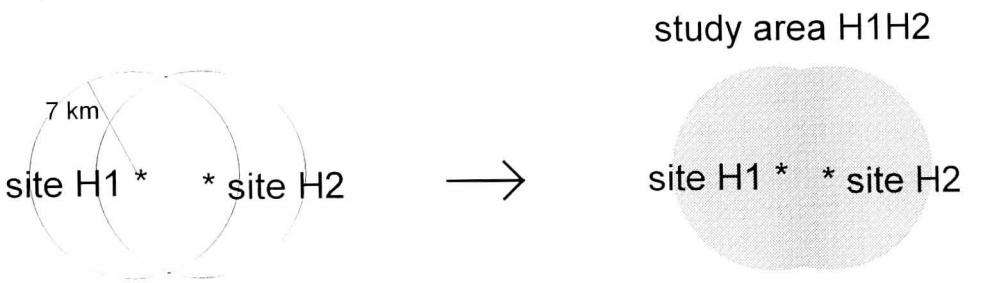
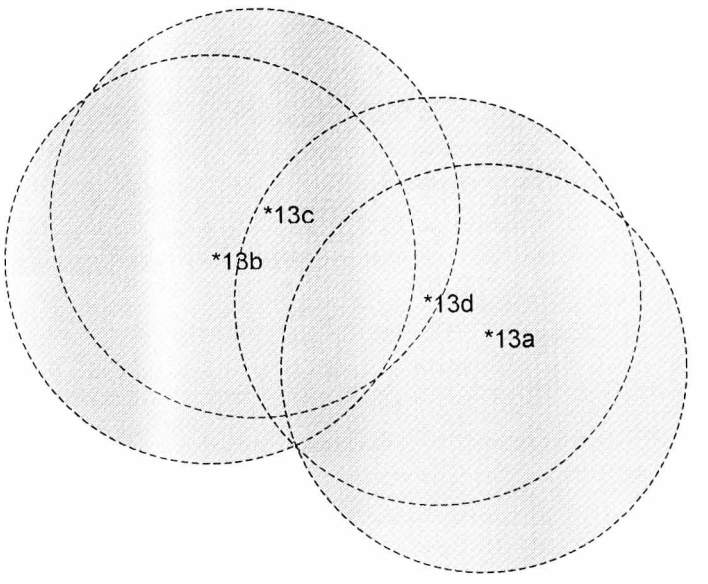


Figure 3.3: Study area 13



iii) Where two sites were very close together and there was no population living between the sites, the sites were considered as one site effectively. A point in the middle of the sites was chosen and the study area defined around this point. In study area 7 three sites were very close together (less than 1 km). The study area was defined as a 7 km circle around a point in the middle of these three sites following method *iii*.

3.3.2 Study periods

For each selected landfill site a study period for the selection of cases and controls was defined, taking account of the five year period considered by landfill experts to be the minimum time period needed for a site to cause significant off-site migration of chemicals (see also section 3.2). Study periods were defined to include cases and controls:

- born before 1 January 1994, and
- born after the start of the malformation registry, and
- born after 5 years of operation of the nearest landfill site.

Table 3.2 shows the study periods relating to each study area. In one centre, Lyon, cases and controls born before 1 January 1995 were included in order to increase the total number of cases and controls in that centre. In Glasgow the study period for both sites in that region was limited to two years, 1991 and 1992, because resources were not available to cover more years. The population size of the Glasgow study areas was large enough to allow for this.

The study period for 3 of the 4 overlapping sites in study area 13 started in 1986, with the start of the Northern Region registry. Site 13d however, opened in 1983 and the start of this site's study period was 1988, according to the above definition. Cases and controls born nearer to site 13d than to site 13a, b, or c, were not included in the period 1986-1987.

3.3.3 Definition of cases

Cases included in the EUROHAZCON study were defined as :

- all live births, stillbirths and induced abortions following prenatal diagnosis;
- registered on one of the participating malformation registers;
- born within the defined study period;
- born to a mother resident in the study area;
- having one of the congenital anomalies on the EUROHAZCON list of anomalies for inclusion (see below);
- with a gestational age of 20 weeks or more, or an induced abortion of any gestational age.

In discussion with the participants a list of anomalies for inclusion in the EUROHAZCON study was drawn up to include all major structural congenital malformations for which a high completeness of case ascertainment could be ensured and to exclude conditions that were not relevant to the study hypothesis. The list of anomalies for inclusion is enclosed in Appendix 5. *Excluded* from this list are the following conditions, unless occurring in combination with other specified anomalies on the inclusion list:

- Minor anomalies. These are anomalies that have little or no serious medical or cosmetic consequences to the child and are relatively frequent. The distinction between 'major' and 'minor' anomalies is often not clear-cut (Dolk and de Wals, 1992; EUROCAT Working Group, 1997). Minor anomalies may be of significance in the study of teratogens (EUROCAT Working Group, 1997), but because of the variable diagnosis and reporting of minor anomalies, many routine malformation registers (including many of the EUROHAZCON participants) cannot ensure a high level of completeness in ascertainment and do not include minor anomalies that occur in isolated form (not associated with major anomalies). All cases with isolated minor anomalies were excluded from this study, using the standard EUROCAT list of minor anomalies (see Appendix 5). Anomalies on this list are for example: ear tags, unspecified cardiac murmurs, patent ductus arteriosus in premature and low birthweight babies, and undescended testicle.

- Deformations. Deformations are anomalies that represent the normal response of a tissue to unusual mechanical forces extrinsic to the fetus, such as uterine constraint (Graham, 1988). Because of their presumed mechanical origin deformations are not usually of interest in the study of possible effects of chemical exposures and are excluded from this study. Deformations include for example club foot and congenital hip dislocation.

- Tumours and neoplasms (teratomas, haemangiomas, etc) and metabolic diseases (including in-born errors of metabolism) were exclude as they do not fall under the usual definition of major structural congenital malformations.

In addition, all cases showing 'familial' transmission were excluded when familial transmission was considered obvious. Cases in which there was doubt about the probability of familial transmission were reviewed by EUROHAZCON participants specialising in medical genetics and paediatrics. Autosomal dominant monogenic syndromes were *in*cluded when there was no obvious familial transmission, since these 'de novo' mutations are of interest in relation to effects of mutagenic chemicals (Czeizel and Kis-Varga, 1987) (see further section 3.4).

Fetal deaths

A large proportion of cases of congenital anomaly abort spontaneously early in pregnancy. For example, the proportion of chromosomal anomalies in recognised miscarriages has been reported to be around 40 percent, whereas these anomalies occur in less than one per cent of livebirths (Kline et al, 1989). The incidence of congenital anomalies in very early spontaneous abortions (before the pregnancy is recognised) is not known. Although early fetal deaths may be of great interest in the study of congenital anomalies, their ascertainment is extremely difficult, if not impossible, especially in routine registration systems. Fetal deaths are commonly only registered after a certain gestational age limit.

In this study, a gestational age limit of 20 weeks was chosen for fetal deaths. This is the limit used by EUROCAT registers. After 20 weeks gestation it is likely that most fetal deaths are examined for congenital anomalies in most participating centres. Although some centres register earlier fetal deaths, these were not included in this study.

Terminations of pregnancy

It is increasingly common for cases of congenital anomaly to be diagnosed prenatally, leading in some cases to termination of the affected pregnancy. EUROCAT figures for example show that 87% of anencephaly cases were terminated after prenatal diagnosis in 1990-1994 (EUROCAT Working Group, 1997). Terminations of pregnancy carried out for congenital anomaly, of any gestational age, were included since the majority of these would have led to inclusion in the study as fetal death (over 20 weeks gestation), stillbirth or live birth. The Slovenia Down Syndrome register does not register terminations of pregnancy.

Multiple deliveries

Twins or multiple deliveries were considered as one "outcome". Where two twins were malformed they were considered one malformed case in analyses. Data on the types of malformations present were collected for both twins. Where one twin was malformed and one normal, the twin pair was again considered as one malformed outcome; the malformed twin was included as a case, the non-malformed twin could not be eligible as a control. Where both twins were non-malformed only one of the twin pair was eligible as a control.

Siblings

Siblings were considered separate outcomes. Both sibs of a sib-pair could be included as case and/or control, *unless* there was obvious familial transmission in two malformed sibs (see above). In case of familial transmission both malformed sibs were excluded.

3.3.4 Definition of controls

Controls were defined as :

- live births and stillbirths;
- born within the study period;
- matched to a case, born on the next day (or nearest day following) to the date of birth of the case, or born in the same year as the case; two controls per case were selected.
- born to a mother resident within the study area;
- verified as *not* having one of the malformations for inclusion;
- with gestational age of 20 weeks or more.

The selection of a spatially unbiased set of controls was essential to the design of this study: selection of controls had to be independent of distance of residence from the waste site within each study area. Controls could therefore not be matched to cases by hospital of delivery as hospital catchment areas may be spatially related to landfill sites, nor by subareas of residence (e.g. municipalities) within the study area. Controls were selected from population-based databases of birth notifications, hospital birth lists, or maternity birth lists. The protocol for control selection emphasised *combining* birth lists of different hospitals, maternities, and administrative districts contributing to births in the study area, *before* performing the control selection. Methods for control selection were tested in the pilot study.

Individual matching by date of birth was performed to ensure standardised control selection methods between centres and to prevent participants having to map all births in a region. Half of the participating centres (Lyon, Antwerp, Tuscany, Slovenia, North East Italy) could not make use of automatic linkage of addresses or postcodes to geographic map references and had to map births manually. Centres were asked to *randomly* select two controls from the births on the nearest day within the study area. In Tuscany only one control per case was selected because of limited resources.

For centres using the U.K. Office for National Statistics (ONS) or the Scottish General Register Office (SGRO) birth database for control selection (Glasgow, Northern Region, England & Wales Down Syndrome register) it was more convenient to select controls as a random sample of all births, matched by the frequency of cases in the same year of birth and same study area, using automatic linkage of postcodes to map locations. The ONS and SGRO birth databases do not include stillbirths so controls in these centres were restricted to live births. Liveborn controls were considered appropriate since the vast majority of cases

would have resulted in a live birth had they not been malformed (the rate of stillbirths is around 5 per 1,000 births).

3.3.5 Data collection

A data transmission form was developed to collect information, for both cases and controls, on basic variables, exposure variables, and potential confounding factors. The data transmission form and accompanying coding instructions are enclosed in Appendix 6. Diagnostic information collected for cases included eight malformation codes, information on syndromes, family history of congenital anomalies, and karyotyping. Malformations were coded according to the British Paediatric Association's perinatal supplement to ICD 9(British Paediatric Association, 1979).

The data transmission form was tested in the pilot study and adapted according to the results of the pilot. Variables which were not commonly available for the majority of centres were not included in the main study. For example, information on racial type, ethnic origin, or country of birth of the mother or father was available only for very few centres and was not included in the main study. In the main study information was collected on two potential confounding factors: maternal age and socio-economic status (see section 3.5).

3.4 GROUPING OF CONGENITAL ANOMALIES

Congenital anomalies form a pathogenically and aetiologically very heterogeneous group of outcomes and analysing all anomalies combined could dilute and conceal relationships between exposure and specific defects or patterns of defects. On the other hand, the requirement to have sufficient statistical power in epidemiological studies does often not allow very specific congenital defects to be investigated. Also, knowledge about aetiology and pathogenesis of congenital anomalies is often too limited to combine individual defects into homogeneous groups. The difficulties in finding a suitable balance between "lumping" and "splitting" of defects for epidemiological analysis have been much discussed (Khoury et al, 1992).

For the current study the EUROCAT subgroup classification, which is based mainly on classification by organ systems, was adapted (EUROCAT Working Group, 1997). The EUROCAT classification was applied to anomalies for inclusion in EUROHAZCON only

(Appendix 5). The EUROHAZCON classification of subgroups is shown in Appendix 7. The subgroup classification was not mutually exclusive; hence cases with multiple anomalies were classed under more than one subgroup.

The main sub-division in the EUROHAZCON classification is between anomalies with a known chromosomal aetiology (structural or numerical), and those of 'non-chromosomal' aetiology. Within the classification of non-chromosomal anomalies the following subgroups were defined differently from the EUROCAT subgroup classification:

- Cardiac malformations were classified according to ICD 10 rather than EUROCAT groups thereby allowing for the separate analysis of anomalies of the cardiac chambers and connections, anomalies of the cardiac septa, anomalies of the cardiac valves, anomalies of the great arteries and veins.

- Multiply malformed cases were classified as those with two or more unrelated major malformations. Multiple central nervous system anomalies, multiple cardiac malformations or multiple renal and urinary anomalies were not considered unrelated. Multiple anomalies included recognised associations such as CHARGE and VATER (Jones, 1988), and excluded monogenic syndromes and sequences of malformations defined below. Multiple malformations are of special interest since most known teratogens have been found to cause patterns of multiple malformations rather than isolated defects (Kallen and Winberg, 1968; Khoury et al, 1994; Khoury et al, 1992).

- Sequences are patterns of malformations that derive from a single common initial anomaly (Spranger et al, 1982). Three specialists in the EUROHAZCON collaborative group classified sequences according to their primary anomaly. Sequences were classed under the group of their primary anomaly only. For example, Goldenhar syndrome was classified only under branchial cleft anomalies and Sirenomelia only under limb reduction anomalies. Three sequences, Pierre Robin (10 cases), Poland (1 case) and Ivemark (1 case), could not be classified because specialists (within the EUROHAZCON collaborative group) did not agree on the primary malformation. Cases with these syndrome were grouped under miscellaneous sequences and not counted under their respective individual defects.

- Monogenic syndromes were presumed to be caused by a sporadic dominant gene mutation when there was no evidence for familial transmission. Members of the EUROHAZCON collaborative group specialising in medical genetics and paediatrics reviewed all syndromes to decide on whether they were sporadic (so called 'de-novo') mutations, or inherited conditions. De-novo mutations are of interest in the study of

possible pre-conceptional mutagenic effects of environmental chemicals (Czeizel and Kis-Varga, 1987; Dolk and de Wals, 1992). Genetic syndromes that occur sporadically and result from dominant single gene mutations have been used as 'sentinel outcomes' for such effects (Czeizel, 1989). Table 3.3 shows syndromes amongst EUROHAZCON cases for which the sporadic (non-familial) form was classified as 'presumed de-novo'.

Table 3.3: Presumed 'de-novo' monogenic syndromes

Syndromes	*Number of cases*
Di George	5
Alagille	1
Bloch-Sulzberger	1
Holt-Oram	1
Arachnodactyly	1
Ichtyosis	1
Marfan	1
Stickler's	1
Aarskog	1
Noonan's	3
Russell-Silver	3
Klippel-Trenaunay-Weber	1
Williams	4
Beckwith-Wiedemann	2
Wiedermann-Rautenstrauch	1
Miller Dieker	1
Angelman	1

All malformations occurring in a malformed twin pair were counted in individual subgroups but not under the multiply malformed, unless more than one malformation occurred in one of the individual twins.

3.5 MEASUREMENT OF SOCIO-ECONOMIC STATUS

Socio-economic status may be an important confounding factor in the relationship between residence near landfill sites and risk of congenital anomaly. There is however no standard method for the measurement and classification of socio-economic status in Europe. Data on socio-economic status available for this study varied considerably between countries. The following information on socio-economic status was collected for the EUROHAZCON cases and controls in the different participating countries:

United Kingdom : As a measure of socio-economic status, cases and controls were given a value for the area-level Carstairs deprivation index (Carstairs and Morris, 1991), by linking

the postcode of residence at birth to census Enumeration Districts (EDs, areas of approximately 150 households). The Carstairs index is calculated from four census variables: overcrowding, social class of head of household, unemployment, and car ownership. EDs were grouped into GB quintiles of deprivation, with quintile 1 containing the most affluent areas and quintile 5 the most deprived.

The Carstairs index has a high and well documented association with health outcomes such as mortality and cancer incidence (Carstairs and Morris, 1991). Area-based deprivation (using the Carstairs index) can discover gradients as large, if not larger than social class based on individual parental occupation in the prevalence of low birth weight (Pattenden et al, 1999).

Denmark (Funen County): Information concerning occupation of the parents was obtained from birth certificates of cases and controls. Occupation of the parents was ranked, blindly to case-control status, using the official Danish system for classifying social class. This ranking has five social classes, 1 is the highest, 5 the lowest. The ranking was done on the highest qualifying occupation of the two parents.

France (Lyon): Information on occupation of the mother was collected for cases and controls. Occupations were grouped according to an official French classification as follows: senior executives and professionals, intermediate occupations and employees, farmers and craftsmen, workmen, unemployed.

Belgium (Antwerp): Census variables were available for districts of 50-1000 households. The census variable average income of the area of residence was used to measure socio-economic status. Average income of the area of residence of cases and controls was classified into quintiles, with quintile 1 containing the highest average income and quintile 5 the lowest.

Italy (Tuscany): In Tuscany information on maternal education was available for both cases and controls. Education was classified as follows: none; elementary, medium, high school, graduate. Maternal education was missing for a relatively high percentage of cases (15.8%) and controls (12.4%). In North East Italy no socio-economic information was available but this centre was excluded from analyses because there were too few cases (section 3.2.2).

Slovenia: Maternal education was available in one of the two study areas. Maternal education was classified as follows: primary, secondary, vocational, high school, university.

3.6 EXPOSURE ASSESSMENT

3.6.1 Distance of residence

In order to investigate whether mothers of cases of congenital anomaly lived closer to hazardous waste landfill sites than mothers of controls, distance of residence of the mother was measured at the time of the birth of the case or control to the nearest landfill site. The use of distance of residence as surrogate of exposure is common in studies of landfill sites and other point sources of pollution (section 2.4).

Place of residence of the mother around the time of conception rather than at birth would have been more appropriate in the study of congenital anomalies, since the critical period for the induction of major structural defects is the embryonic period in the first trimester of pregnancy (section 2.3). The period before conception may be important for the induction of mutagenic effects or for chemicals that accumulate in the body. In this last case length of residence before pregnancy near the landfill may be important. In most of the participating centres there was no information either on the address of the mother at the time of conception or on length of residence in the study area. Distance of residence at birth was therefore used in all centres.

Geographic locations of residence of the mother at the time of birth were obtained in the U.K. centres by linking postcodes to grid references, in Funen County by linking addresses to grid references, and in the other centres by manually plotting addresses on a map. The accuracy for obtaining geographic co-ordinates was 100 metres or better.

Study areas were dichotomised into a 0-3 km proximate zone of 'most likely exposure to the landfill site' and a 3-7 km distant or 'unexposed' zone. The 3 km cut-off was decided a-priori (before the start of analyses) on advice of landfill experts who considered this distance would include the extent of any significant exposure. More detailed distance zones (0-1, 1-2, 2-3, 3-4, 4-5, 5-7 km) and continuous distance were also analysed as exposure measure.

3.6.2 Hazard scoring of landfill sites

The potential of a landfill site to cause contamination of the surrounding environment and exposure of nearby residents depends on a wide range of site specific conditions as discussed in section 2.1. This section describes the methodology used to classify EUROHAZCON study sites according to the potential exposure hazard they pose, relative to each other, in order to provide more detail to distance based exposure assessment. The classification will be used to investigate whether sites with a greater potential hazard are associated with a greater risk of congenital anomaly in their vicinity.

The classification of EUROHAZCON study sites according to their hazard potential firstly involved the development of a methodology for hazard potential scoring. Existing U.S. site ranking systems, reviewed in section 2.1, almost all require detailed information about concentrations of chemicals on and off-site in different environmental media. In order to apply such systems to the EUROHAZCON study sites, either extensive monitoring data would need to be available, or site investigations would have had to be carried out as part of the study. Monitoring data were available for most of the study sites but not in a form which could readily be summarised and compared between sites (see further section 4.3.1 of the results). It was not feasible to conduct site investigations or environmental monitoring within the scope of the EUORHAZCON study. Hence, the EUROHAZCON hazard potential scoring methodology had to use existing information on site characteristics that would affect the likelihood of off-site contamination, rather than measurements of actual chemical concentrations on or off-site.

Two hazard scoring methods were assessed and compared for their use in this study: an adaptation of the existing site ranking methodology developed by JRB Associates (JRB Associates, 1982), and scoring of sites by a panel of landfill experts. After comparison of the two methods the expert panel scoring was judged by the landfill experts to be more valid than the adapted hazard scoring system. The experts felt that complicated relationships between factors were better reflected in the expert panel scoring than in the adapted JRB scoring system (see further Appendix 8). The expert panel scoring was therefore used for the final classification of sites. The adapted JRB scoring system and the comparison of the two systems are described in detail in Appendix 8. The expert panel scoring methodology is described in the following sections (3.6.2.1, 3.6.2.2)

3.6.2.1 Landfill Site Ranking Questionnaire

Firstly, a Landfill Site Ranking Questionnaire was developed to collect existing information on site characteristics necessary for both the adapted ranking system and the expert panel scoring. The landfill ranking questionnaire included information on factors which can influence the likelihood of off-site contamination occurring, on evidence that such contamination had occurred, and on conditions affecting the likelihood that nearby human residential populations would come into contact with potential contamination from a site. The landfill ranking questionnaire was designed with the help of one landfill specialist (Patrick Pointer) to include information which would be relatively readily available for the majority of sites from documentation held by the waste site regulator, operator, inspector, and/or other relevant parties. Existing landfill site questionnaires were used as example for the format of some of the questions (Croft and Campbell, 1990; Department of the Environment, 1995). The questions were designed also to allow for the application of the different rating scales in the adapted ranking system (see Appendix 8).

Table 3.4 shows the main items included in the landfill site ranking questionnaire. The full questionnaire is included in Appendix 9. The first-stage questionnaire that was used to identify sites for inclusion in the study (the 'questionnaire for characterisation of landfill sites'), covered many of the same items but in less detail (section 3.2.2, Appendix 4). Some items, such as the start and closure dates of the site, were not included in the ranking questionnaire because they had already been included in the characterisation questionnaire.

In each study region a local landfill specialist collaborated with the participating centre to complete the questionnaires. The local specialists were employed by local waste authorities responsible for regulation and/or monitoring of the sites (equivalent to the local U.K. Environment Agency). Questionnaire response is described in detail in results section 4.3.1.

Questionnaires were completed for 25 of the 28 EUROHAZCON study sites. Questionnaires for sites selected in study regions for the England & Wales Down Syndrome Register (sites 18, 19 and 20) were not completed in time to be included in the hazard scoring.

Table 3.4 : Items included in the Landfill Site Ranking Questionnaire

Items included in questionnaire
Total site area
Total quantity of waste in place: volume or weight, depth
Hazardous waste' quantity or % of total waste classified as 'hazardous'
Types of hazardous and industrial waste deposited
Containment / lining
Covering
Capping
Leachate collection system
Leachate monitoring
Soil Type and permeability
Groundwater depth
Groundwater monitoring
Groundwater contamination
Public drinking water supply extraction points within 3 km
Private water supply extraction points within 3 km
Surface water: type and distance
Surface water monitoring
Surface water contamination
Landfill gas control system
Landfill gas monitoring
Landfill gas migration
Complaints about smells and odours from the landfill
Rainfall
Landuse for recreation and/or food consumption within 3 km

3.6.2.2 Expert panel scoring

The answers to the ranking questionnaire were summarised in a document containing descriptions of each study site for which the questionnaire had been completed. This summary description document was sent to the members of an expert panel made up of four local landfill advisers (one who also assisted in the development of the JRB adaptation, one who helped with the development of the questionnaire and the JRB adaptation). Two of the experts worked for regional environment agencies (in Scotland, Denmark, and Italy) and two for waste disposal companies (in England). Three experts were involved in the regulation and/or monitoring of sites included in the EUROHAZCON study (site 15a and 15b in Glasgow, sites 21 and 22 in North East Italy, and sites 1 and 2 in Funen County, Denmark)

Each expert was asked to score each landfill site relative to the other sites on the basis of the information provided in the site descriptions. The experts were blind to results of analyses of risk of congenital anomaly in relation to distance from each site. Sites were scored on a scale from 1 (low hazard) to 5 (high hazard) in three categories: water, air, and overall. The *water hazard* scoring aims to reflect the ease with which hazardous materials can escape via the water route (groundwater and surface water), and the potential for the

nearby population to come into contact with the water (via drinking water, surface water, recreation). The *air hazard* scoring aims to reflect the ease with which hazardous substances in both vapour and particle form may be emitted into the air. The *overall hazard* scoring aims to reflect a site's overall potential to cause exposure of nearby residents relative to other sites. A large, old, badly managed site with many reported problems for example, would receive a higher overall score than a well-managed, small site. Table 3.5 shows the scoring guide that members of the expert panel were sent with the site description document.

A meeting was held with the four members of the expert panel to discuss the expert scoring and to decide on a method for the final scoring of the EUROHAZCON study sites. In this meeting experts first discussed reasons for differences between the experts' scores on a site-by-site basis, and were given the chance to consult additional documentation on the site such as inspection and monitoring reports. In the site-by-site comparison of experts' scores, experts were given the chance to change their scores on the basis of the discussion with other experts or extra information presented at the meeting. Scores were changed mainly for the following reasons: when discussion between experts led to a consensus, when first-hand knowledge from one of the experts changed the opinion of the others, or when the information given in the summary description proved to be misinterpreted by one or more of the experts. As an example of the latter, one site was judged of low air hazard by one expert because a gas collection system was present, whereas the other experts had noted that the gas collection system was installed after the study period ended and scored the air hazard higher. The first expert increased his score at the meeting. As an example of first-hand knowledge leading to a change in scores, a site for which groundwater pollution had been detected and which was near a drinking water well was judged of high water hazard by three experts. First-hand knowledge of the fourth expert clarified that the groundwater flow was away from the drinking water well and the others lowered their scores.

The hazard potential classification of EUROHAZCON study sites was based on the average of the four experts' final scores, final referring to scores after changes were made at the meeting. Results of the scoring and classification of the study sites are presented in section 4.3.2.

Table 3.5: Expert panel scoring guide

Hazard in relation to WATER pathway:
Leaching and run-off of chemicals from the landfill site may cause ground and surface water contamination which would form a hazard for residents via drinking water consumption, other domestic water uses, and use of land in the vicinity of the site (i.e. food growing, recreation). The hazard scoring related to this water pathway reflects the ease with which hazardous materials can escape via the water route, and the potential for nearby population to come into contact with the water (via drinking water, surface water, recreation). Factors such as drinking water supply, land use, soil characteristics, distance to groundwater and surface water, and management practices such as leachate collection, lining of the site, monitoring and contamination of groundwater and surface water, are documented in the Site Description Document.

WATER hazard scoring guide:

1	2	3	4	5
Low hazard		**Medium hazard**		**High hazard**
- Evidence of no contamination of ground or surface water, or - No water monitoring performed, but low potential hazard based on available information (site engineering, soil type, management of the site, size of the site, etc.).		- Evidence for some off-site contamination of ground- or surface water, and/or some potential for drinking water contamination, or - No, or limited water monitoring performed, but medium potential for off-site contamination on basis of other available information.		- Evidence of high off-site contamination of ground and/or surface water, and/or potential for drinking water contamination, or - No, or limited water monitoring performed, but high potential hazard relating to the water pathway based on available information.

Hazard in relation to AIR pathway:
Landfill sites may be a source of airborne toxic chemical contamination by evaporation or via windblown particles. The hazard scoring of the air pathway reflects the ease with which hazardous substances in both vapour and particle form may be emitted into the air. Migration of landfill gas is of importance because it may carry along waste vapours, such volatile organic substances. Factors such as the presence of a gas collection system, evidence of gas migration, and evidence of migration of other substances, are documented in the Site Description Document. Waste management practices such as capping and covering of the site are important in relation to the potential of dust and particles being blown off-site.

AIR hazard scoring guide:

1	2	3	4	5
Low hazard		**Medium hazard**		**High hazard**
- Evidence of no off-site migration of landfill gas or air pollutants, or - No air monitoring performed, but low potential hazard based on information available (site engineering, quantities of waste, age of site, etc.).		- Evidence for some off-site migration of gas or air pollutants, or - No, or limited air monitoring, but medium potential for off-site contamination on basis of available information.		- Evidence of off-site migration of high levels of landfill gas and/or other air pollutants or, - No, or limited air monitoring performed, but high potential hazard based on other available information.

OVERALL hazard potential :
The scoring of the overall hazard of the sites reflects the overall potential of a site to cause exposure of nearby residential populations. A large, old, badly managed site with many reported problems would get a high overall score and a well-managed, small site with no reported problems would be assigned a low overall hazard score. Factors such as age of the site, size of the site, quantities of waste present, actions taken to prevent leachate and landfill gas emissions, adequacy of the monitoring at the site, and contamination problems, are documented in the Site Description Document.

OVERALL HAZARD SCORING GUIDE:

1	2	3	4	5
Low hazard		**Medium hazard**		**High hazard**
- Relatively new well-managed site with few reported problems. - Relatively small quantity of waste in place. - Adequate measures to prevent gas and leachate migration in place since start of site. - Adequate monitoring of the site.		- Site of medium size and age. - Some reported problems. - Adequate measure to prevent gas and leachate migration have been taken over time / some measures have been taken but not adequate. - Some monitoring, but not adequate.		- Site with large quantities of waste and/or old, uncontrolled site, and: - No measures taken to prevent off-site migration of landfill gas or leachate. - No routine monitoring. - Many problems reported.

3.7 STATISTICAL ANALYSIS

3.7.1 Distance of residence

The association between distance of residence from hazardous waste landfill sites and risk of congenital anomalies was investigated using logistic regression models (Breslow and Day, 1980), and related binomial models for the modeling of continuous distance (see below).

In all analyses (those of non-chromosomal anomalies, chromosomal anomalies and malformation subgroups) the total pool of controls for the relevant study area(s) was used. Analyses of chromosomal anomalies were carried out both including and excluding data (cases and controls) from the Slovenia and England & Wales Down Syndrome register study areas. Controls from the Slovenia and England &Wales Down Syndrome Register study areas were not included in any non-chromosomal analyses.

Individual matching by date of birth was carried out for administrative convenience rather than to control for confounding. Therefore, unmatched (unconditional logistic regression) analyses were carried out, but terms for study area and year of birth were included in all models described in sections 3.7.1 and 3.7.2.

3.7.1.1 Control for confounding factors

The potential for socio-economic status and maternal age to confound the relationship between proximity to landfill sites and risk of congenital anomaly was assessed firstly by calculating the odds ratios for congenital anomaly (non-chromosomal and chromosomal) in social classes and maternal age groups, adjusted for distance from waste site. Also, the social class and maternal age distribution of controls with distance from the waste sites were described. Maternal age analyses were carried out pooling data for all centres, social class analyses were done separately for each of the non-U.K. centres. In U.K. centres the relationship between socio-economic status and risk of congenital anomaly was analysed in more detail as described in section 3.7.3.

Subsequently, socioeconomic status and maternal age were included in all logistic and binomial regression models as covariates. Information routinely available on socio-economic

status (SES) varied greatly between countries participating in the study as discussed in section 3.5. When adjusting for socio-economic status in analyses in which study areas were pooled, SES was therefore modelled separately, as a categorical variable (1, 2, 3, 4, 5, unknown), in each country. This allowed for the relationship between socio-economic status and the risk of congenital anomaly to be different in each country. When adjusting for maternal age, age groups (<20, 21-24, 25-29, 30-34, >=35 years) were modelled as categorical variables.

3.7.1.2 Dichotomous distance

As was discussed in section 3.6.1 distance of residence to the nearest waste site was first dichotomised into a 0-3 km 'proximate' zone, and a 3-7 km 'distant' zone. Odds ratios for living within 0-3 km compared to 3-7 km were calculated in each study area separately and for all study areas pooled, both for non-chromosomal anomalies combined and chromosomal anomalies combined. Analyses of malformation subgroups were carried out pooling data for all study areas. Malformation subgroups with 20 or more cases were analysed.

The estimation of pooled odds ratios, combining all study areas, can be problematic if odds ratios for different study areas are not homogeneous, i.e. if they are not part of the same underlying distribution. Analogous problems in meta-analyses have been much discussed (DerSimonian and Laird, 1986; Pocock, 1993; Thompson, 1993; Thompson, 1995). In order to test whether odds ratios showed heterogeneity between study areas, and therefore whether the pooling of all study areas was appropriate in this study, likelihood ratio tests for the interaction between study area and distance to a waste site (0-3 km, 3-7 km) were carried out. Statistical tests for heterogeneity are generally not very powerful and can only tell whether major heterogeneity is present or not (Pocock, 1993; Thompson, 1995). Even in the absence of major heterogeneity, some variability may still exist between effects in different study areas. Such variability is not taken into account in the conventional logistic regression models described above. If variability between study areas exists, the confidence intervals calculated through these conventional, so-called 'fixed', models are narrower, suggesting a stronger association, than if variability were taken into account. Random effects models can be applied which do allow for effects (log odds ratios) to vary between study areas and calculate more accurately the confidence interval around a pooled odds ratio. Random effects models are part of the family of 'multi-level' models developed to deal in general with any data of clustered or hierarchical structure (Goldstein, 1995). Several

"random-effects" approaches were applied to the pooled data in close collaboration with statisticians advising the EUROHAZCON project. Bayes random effects modelling was carried out by statisticians in the Environmental Epidemiology Unit.

3.7.1.3 Continuous distance

Analyses of continuous distance were carried out for all study areas pooled, both for non-chromosomal anomalies combined and for chromosomal anomalies combined. Standard logistic models were fitted first, modeling distance (D) and the reciprocal of distance(1/D).

The absence of adequate exposure information makes it difficult to specify which function would be most appropriate to model a possible decline in risk with distance. In the case of landfill sites it appears that if contamination occurs, it is likely to occur close to a site and disperse quickly as distance from the site increases (section 2.2). Thus, a high risk near the site which decreases faster nearer the site than further away seems a reasonable assumption. Therefore, several models in which excess risk (odds ratio) declines exponentially with increasing distance from a landfill were fitted in addition to the standard logistic models. As described by the EUROHAZCON collaborative group (Dolk et al, 1999), models of this type are part of a family of non-linear 'excess relative risk' models described previously to model relationships between radiation dose and cancer in A-bom survivors (Pierce and Preston, 1985; Pierce et al, 1996) and proposed independently to model risk around point sources of pollution in case-control studies (Diggle and Rowlingson, 1994).

The following model was fitted :

$$\pi/(1-\pi) = \exp(\beta_i x_i)\{1 + \alpha\exp(-\gamma d)\}$$

In this function π is the probability of being a case. In the first part of the equation ($\exp(\beta_i x_i)$) confounding covariates are modelled as a logistic function. The relationship between continuous distance and excess risk over and above this baseline function, is modelled by $\{1 + \alpha\exp(-\gamma d)\}$ where d=distance from waste site, γ defines the rate of decline in excess risk (OR) with distance, and α defines the maximum excess risk (right next to the site) relative to being distant from it ($d \rightarrow \infty$). Models were also fitted with distance squared (d^2), in which risk declines more steeply with increased distance.

3.7.2 Hazard scoring analysis

3.7.2.1 Agreement between experts

In order to assess the agreement between experts in both initial (before changes) and final (after changes were made at the meeting) expert hazard potential scores, intra-class correlation coefficients (ICC) were calculated by analysis of variance (STATA command loneway, (Stata Corporation, 1997)). In addition, the reliability of the average expert scores (ICC_k) was calculated. ICC and ICC_k are calculated as follows (de Cock et al, 1996; Winer, 1971):

ICC = variance between sites / (variance between sites + variance within sites)
= inter-rater agreement = reliability of single rater;

ICC_k = variance between sites / ((variance between sites + variance within sites)/*k*)
= reliability of mean of *k* raters = reliability of the average score.

An intra-class correlation coefficient (ICC) of 1 reflects perfect agreement between experts; an intra-class correlation coefficient of 0.5 reflects as much variation within sites as between sites.

The average score of a number of raters becomes more reliable (i.e. more repeatable) the more raters are used, regardless of how good the agreement is between the raters. This is reflected in ICC_k. ICC_k is calculated under the assumption that four component scores represented independent assessment (Winer, 1971). This assumption is only partly true for the average *final* hazard scores since experts changed scores after discussion at the expert panel meeting. The reliability of the average final hazard scores could therefore be overestimated using the above calculations.

Correlations between water, air, and overall hazard scores, and initial and final scores were calculated using Pearson correlation coefficients.

3.7.2.2 Trend in odds ratios with hazard potential

This section describes statistical methods used to investigate whether sites classified as posing a greater potential hazard through the expert panel scoring, are those associated with a greater risk of congenital anomaly nearby the site compared to further away. These

analyses investigate whether the hazard potential of a site *modifies* the odds ratio for residence within 0-3 km from sites, using the same distance cut-off as in previous dichotomous analyses (section 3.7.1.2).

The hazard potential of each site was classified according to average final hazard scores (for overall, water, and air hazard), as discussed in section 3.6.2.2. In study areas containing more than one site, different hazard scores were given to different sites which made the assignment of one score to the exposure zone in those study areas problematic. It was decided that if 3 km 'exposure' zones around sites did not overlap in these multiple-site areas the average hazard score of the sites, weighted by the proportion of controls nearby each site, most accurately represented the hazard of the exposed zone in the study area. If the 3 km zones did overlap the score of the *highest* scoring site was applied to the exposed zone. This was done on advice of landfill experts, although they admitted not being very confident about their assessment of how hazards from multiple sites would affect exposure of residents in an area.

The association between risk of congenital anomaly near a site and hazard potential of a site was investigated by analysing the trend in odds ratios for living within 3 km from a site with hazard potential of a site. This trend was analysed in two ways:

a) Using hazard categories: high, medium, and low hazard categories were created using tertiles of the hazard scores as cut-off points. In each of the three hazard categories the odds ratio for living within 3 km from a waste was calculated. The likelihood ratio test for the interaction term between hazard category as a numerical variable (1=low, 2=medium, 3=high) and distance zone (0-3 km vs. 3-7 km) was then used to test for the statistical significance of the trend in odds ratios from low to high hazard category

b) Using continuous hazard scores : rather than high, medium, and low hazard categories continuous hazard scores of study areas were modelled. The likelihood ratio test for the interaction between continuous hazard score (for each study area) and distance zone (0-3 vs. 3-7 km) was again used to test for the statistical significance of the linear trend in the odds ratios with hazard score. In this linear model each unit increase in hazard score leads to a unit increase in the log odds ratio.

All the above analyses were adjusted for maternal age and socio-economic status.

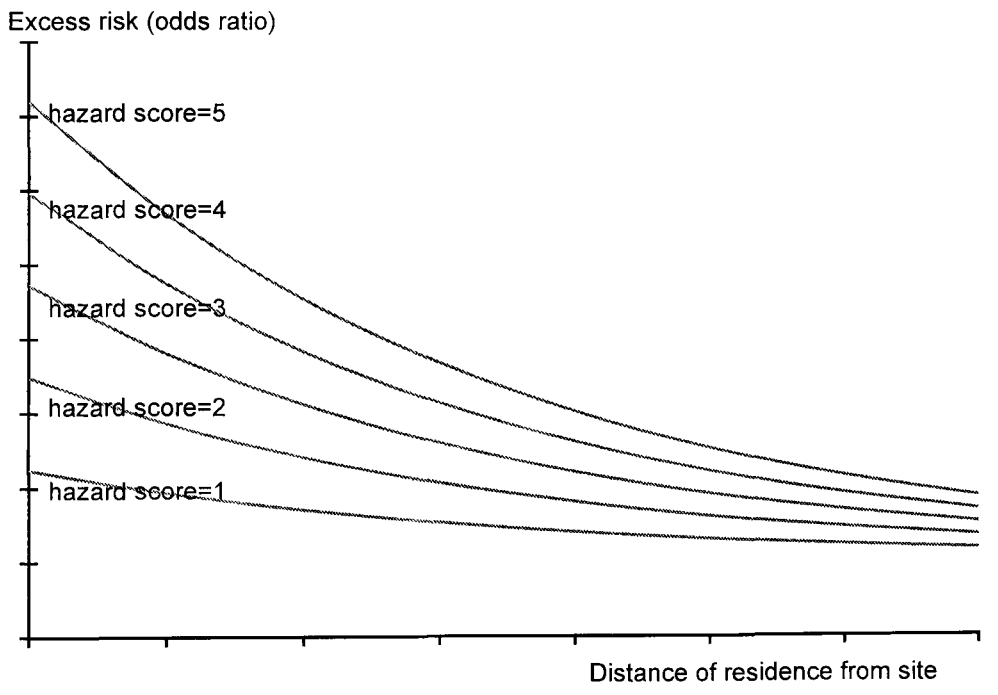
3.7.2.3 Hazard potential score in continuous distance models

This section describes exploratory analyses which incorporate hazard potential scores in the model of exponentially declining excess risk with continuous distance from site, as described in section 3.7.1.3. The following exponential excess risk model was fitted :

$$\pi/(1-\pi) = \exp(\beta_i x_i) \{1+ (\alpha H) \exp(-\gamma d)\}$$

In analogy with the model fitted in section 3.7.1.3, π is probability of being a case, $\exp(\beta_i x_i)$ a vector of confounding covariates, and d the distance of residence from the nearest waste site. Again, γ defines the rate of decline in excess risk with distance and is in these analyses fixed at a value of 0.28, the rate of decline found in models including distance only (results section 4.2.3). H is the hazard score of the site, rescaled to range from 0.2 to 1 (originally 1 to 5). The lowest hazard sites have score 0.2 and the highest hazard sites have score 1. α again defines the maximum risk right next to the site but in this model the risk right next to the site is proportioned according to the hazard score following the linear function (αH). This assumes that each unit increase in hazard potential score leads to a unit increase in malformation risk right next to the site. Figure 3.4 shows how the introduction of the hazard score affects the exponential excess risk model.

Figure 3.4: Incorporating hazard potential scores in the exponential excess risk model.



The log likelihood of the model including the hazard score was compared to the model not including the hazard score by calculating the likelihood ratio of the two models. It is not

possible to test for statistical significance in the difference between two models with equal numbers of parameters, as is the case here, since such a test would have zero degrees of freedom. Likelihood ratios can be used to informally compare models with equal numbers of parameters to give some indication as to which model fits the data better (Walker and Rothman, 1982). Interpretation is, however, very difficult without formal statistical tests available. Therefore, these analyses are presented as 'exploratory' and should be seen only as a possible basis for further development.

The above analyses were carried out only for non-chromosomal anomalies.

3.7.3 Socio-economic variation in risk of congenital anomalies

One of the objectives of this thesis is to examine the extent to which socio-economic status is a risk factor for congenital malformations, including specific malformation subgroups, since little is known from the literature about the presence or absence of a socio-economic gradient (section 2.5). Data from the four U.K. participants in EUROHAZCON were pooled to investigate socio-economic variation in congenital anomaly risk, since in these centres socio-economic status was based on the same measure: area deprivation based on the Carstairs index (section 3.5).

The association between deprivation and risk of congenital anomaly in the U.K. centres was investigated by including deprivation quintile as a numerical variable in logistic regression models, assuming a (log-)linear relationship between deprivation quintile and risk of congenital anomaly. This assumption seemed justified since there was no statistically significant difference in the fit of models (for all malformations combined) treating deprivation quintile as a categorical and as a numerical variable. The models treating deprivation quintile as a numerical variable allowed for the estimation of odds ratios in the deprivation quintiles even when numbers of cases in certain quintiles were zero, which was the case for some of the smaller malformation subgroups. Odds ratios in quintile 5 (most deprived) compared to quintile 1 (most affluent) were estimated from slope parameters produced in the log-linear models. The likelihood ratio test was used to test for linear trend in the effect of deprivation.

Analyses were controlled for region, year of birth, maternal age (<30, 30-34, >=35), and distance of residence from a landfill site (<3 km, 3-7 km), which had previously been shown to be related to congenital anomaly risk (see section 4.2). Analyses were carried out for all non-chromosomal anomalies combined, all chromosomal anomalies combined, and malformation subgroups which contained 20 or more cases.

CHAPTER 4

RESULTS

4.1 DESCRIPTION OF STUDY SITES AND STUDY SUBJECTS

The results in this chapter are based on a total of 1089 non-chromosomal cases, 270 chromosomal cases, and 2508 controls, selected in 20 study areas around 26 hazardous waste landfill sites (Table 4.1). Analyses of non-chromosomal anomalies (section 4.2) and hazard scoring analyses (sections and 4.3 and 4.4) used data from study areas 1 to 15. Analyses of chromosomal anomalies (section 4.2) used data from study areas 16-20 also. Three study areas (7, 13, and 15) contained more than one site (section 3.3.1).

Table 4.1: study areas, study sites, study periods, and numbers of cases and controls

participating centre	*study areas*	*study sites*	*study period*	*non-chromosomal cases*	*chromosomal cases*	*controls*
Funen County (Denmark)	1	1	1987-93	19	3	44
	2	2	1986-93	28	6	68
North Thames (West) (UK)	3	3	1990-93	50	12	124
	4	4	1990-93	10	5	30
Lyon (France)	5	5	1990-94	35	4	78
Antwerp (Belgium)	6	6	1990-93	73	7	160
	7	7a, b, c	1990-93	35	6	82
	8	8	1992-93	6	2	16
Tuscany (Italy)	9	9	1982-93	60	7	67
	10	10	1982-93	121	17	138
	11	11	1987-93	45	8	53
Northern Region (UK)	12	12	1989-93	120	28	300
	13	13a, b, c, d	1986-93	296	63	740
	14	14	1990-93	23	6	58
Glasgow (UK)	15	15a, b	1990-91	168	30	408
Subtotal for non-chromosomal and hazard scoring analyses:				[1089]	[204]	[2366]
Slovenia	16	16	1989-93		15	30
	17	17	1988-93		4	8
England&Wales Down Syndrome Register	18	18	1989-92		9	18
	19	19	1989-92		8	16
	20	20	1989-93		30	70
Total number	20	26		1089	270	2508

4.1.1 Study sites

Table 4.2 presents basic descriptions of the 26 EUROHAZCON study sites included in analyses. More detailed site descriptions, based on the landfill ranking questionnaire are given in section 4.3.1.

The majority of the study sites were operational during the study periods. Around one third of sites (9) closed before the start of the study period. Four of these sites closed a long time ago, at the end of the 60s or beginning of the 70s. The other five sites closed during the middle to late 80s. Sites included in the study were generally quite old: 18 sites started 20 or more years before the end of the study period, 6 started 10 or more years before the end of the study period, and only 2 sites (site 12 and 14) opened less than 10 years before the end of the study period.

Landfill regulations started to be tightened up in the late 1970s to early 1980s in many European countries. European Community (EC) legislation on hazardous waste management first came out in 1978 although often not with immediate impact(Brand, 1993). The majority of study sites predate EC legislation: 21 opened before 1980 and only five sites opened after 1980.

The landfill sites included in this study varied greatly in size. The total site area ranged from 1 to over 300 hectares. The majority of sites (18 out of 26) were under 15 hectares in size, while 3 sites were 100 hectares or larger.

Landfill sites were selected for this study on the basis that they contained 'hazardous' waste of non-domestic origin. Most of the study sites contained other waste types besides industrial hazardous waste: 19 sites had taken a mix of inert, household, commercial, and industrial wastes. At seven sites (site 4, 7a, 7b, 9, 10, 11, 15b, 17) only industrial wastes had been deposited, in some cases mixed with inert or demolition wastes. Some of these (4, 7a, 7b, 11, 15b) were old and relatively uncontrolled dumps associated with specific industrial operations (i.e. chromium production, copper production).

Table 4.2: Basic description of EUROHAZCON landfill sites

site	*operational years*	*open or closed at start of study period*	*total site area*	*broad waste types*
1	1962-72	closed	1.1 ha	inert, household, commercial and industrial wastes
2	1950-74	closed	2.2 ha	household and industrial waste
3	pre1961-present	open	31 ha	household waste, construction waste, industrial and special wastes
4	1956-85	closed	1.42 ha	construction and demolition wastes, industrial liquid and solid wastes
5	1979-88	closed	10 ha	inert waste, household, commercial and industrial wastes, including hazardous wastes and sludges
6	1964-86	closed	4.6 ha	inert, household, industrial wastes
7a	1955-60	closed	10 ha	industrial wastes: residues from copper prodcution
7b	pre1970-pre1990	closed	2.1 ha	industrial wastes from copper production
7c	1953-present	open	14.6 ha	inert, household, industrial and chemical wastes
8	1966-present	open	100 ha	household wastes, building and demolition wastes, industrial wastes
9	1978-84	open	2 ha	inert waste, industrial wastes
10	1974-83	open	7.6 ha	incinerator waste, fly-ash, and contaminated soil/sludges
11	pre1950-85	closed	1 ha	hazardous solids: heavy metals.
12	1984-94	open	2.7 ha	household, commercial, industrial, and special and restricted wastes
13a	1972-present	open	6.5 ha	inert, household and commercial, general industrial, and special wastes
13b	1973-89	open	12.5 ha	inert, household and commercial, general industrial, and special wastes
13c	1981-94	open	7.1 ha	inert, household and commercial, general industrial, and special wastes
13d	1983-93	open	10.1 ha	inert, household and commercial, general industrial, and special wastes
14	1985-present	open	4.5 ha	inert, household and commercial, general industrial, and special wastes
15a	1955-present	open	29 ha	construction and demolition materials, household, commercial and industrial waste, special and notifiable waste
15b	1935-68	closed	2.5 ha	waste from chemical works and chromium processing industry, demolition products
16	1963-present	open	54 ha	inert, household, commercial, industrial waste
17	1983-present	open	6 ha	industrial wastes
18	pre70-present	open	284 ha	domestic, industrial, special wastes
19	~1900-present	open	365 ha	commercial and household wastes, liquid and solid hazardous wastes
20	1930-present	open	37 ha	household, commercial, industrial, special wastes

4.1.2 Cases and controls

After exclusion of cases that did not have a congenital anomaly on the list of anomalies for inclusion, there were 1089 cases of non-chromosomal aetiology and 270 chromosomal cases available for analysis (Table 4.1). The largest proportion of cases (40% of non-chromosomal and 36% of chromosomal cases) were from study areas in the Northern Region (U.K.). Approximately two non-malformed controls were selected per case in most

centres with the exception of Tuscany where the case-control ratio was 1:1. In centres that carried out frequency matching rather than individual case-control matching (Northern Region, Glasgow, England & Wales Down Syndrome Register) an exact 1:2 case-control ratio was not always maintained since controls for excluded cases remained in the data.

Type of birth

Table 4.3 shows the type of birth of cases and controls. Eighty five percent of non-chromosomal and 74% of chromosomal cases were live births. This is similar to the percentage of livebirths in data from the European Network of Congenital Anomaly Registers, EUROCAT, which reports 87% of livebirths amongst all their cases of congenital anomaly and 62% amongst Down Syndrome cases (EUROCAT Working Group, 1997). Terminations of pregnancy following prenatal diagnosis were included as cases in all centres apart from Slovenia. Overall 11% of non-chromosomal cases were terminations, ranging from 0% (in Funen) to 20% (in North West Thames). The proportion of terminations was considerably higher amongst some specific defects, for example neural tube defects (61%). Twenty four percent of chromosomal cases were terminations, ranging from 3% (in Tuscany) to 75% (in Lyon).

All controls are live births. Although in all centres apart from Glasgow, Northern Region, and the England & Wales Down Syndrome register, stillbirths were available for the selection of controls, by chance no stillborn controls were selected for the study. Stillbirths occur in around 5 per 1,000 births so in the centres where stillborn controls could be selected one would expect only a small number of stillbirths (total of 4-5 stillbirths in 898 control births).

Table 4.3: Type of birth

	non-chromosomal cases	*chromosomal cases*	*controls*
Live births	929 (85%)	200 (74%)	2508
Stillbirths and foetal deaths	40 (4%)	5 (2%)	
Terminations	117 (11%)	64 (24%)	
Not known	3	1	

Malformation subgroups

Table 4.4 shows the frequency of malformation subgroups in non-chromosomal and chromosomal cases. The largest subgroups of non-chromosomal anomalies are cardiac malformations (group 7-10: 35%), neural tube defects (group 1: 12%), and oral clefts (group

13: 10%). Seventy two per cent of chromosomal cases were cases of Down Syndrome. Only subgroups with 20 or more cases were analysed in relation to distance from waste sites (section 4.2). Gastroschisis and exomphalos are both classed in the group of abdominal wall defects but have very different risk factors (Tan et al, 1996) and are therefore thought to have different aetiologies. Hence, these defects were analysed separately, even though numbers of cases were smaller than 20.

Table 4.4 : Frequency of malformation subgroups

subgroup		*N*	*%*	*subgroup*		*N*	*%*
NON-CHROMOSOMAL ANOMALIES				*CHROMOSOMAL ANOMALIES*			
1	Neural tube defects	130	11.9	31a	Downs syndrome	195	7
2	Hydrocephaly	32	2.9	31b	Non-Downs syndrome chromosomal anomalies	75	2
3	Microcephaly	12	1.1		Patau's syndrome (trisomy 13)	9	3
4	Other specified brain anomalies	11	1.0		Edwards's syndrome (trisomy 18)	22	8
3 + 4	Other central nervous system anomalies	23	2.1		Autosomal deletion syndromes	6	2
5	Eye anomalies	6	0.6		Other conditions due to autosomal anomalies	18	6
6	Ear anomalies	5	0.5		Gonadal dysgenesis (Turner's syndrome)	11	4
7	Malformations of cardiac chambers and connections	45	4.1		Klinefelter's syndrome	3	1
8	Malformations of cardiac septa	248	22.8		Other conditions due to sex chromosome anomalies	3	1
9	Malformations of valves, and other heart malformations	109	10.0		Conditions due to anomaly of unspecified chromosome	3	1
10	Anomalies of great arteries and veins	98	9.0				
10a	Anomalies of great arteries and veins: excl PDA	63	5.8				
7 to 10	All cardiac anomalies	384	35.3				
11	Anomalies of respiratory system	14	1.3				
12	Choanal atresia + other nose anomalies	14	1.3				
13	Cleft palate and cleft lip	109	10.0				
13a	Cleft palate	38	3.5				
13b	Cleft lip with or without cleft palate	72	6.6				
14	Tracheo-oesophageal anomalies	25	2.3				
15	Digestive system and upper alimentary tract	59	5.4				
16	Atresia and stenosis of rectum and anal canal	20	1.8				
17	External genitalia (male): hyposadias	45	4.1				
18	External genitalia (female + indeterminate)	10	0.9				
19	Renal anomalies	75	6.9				
20	Urinary tract anomalies	69	6.3				
21	Limb reduction defects	41	3.8				
22	Branchial cleft anomalies	5	0.5				
23	Other musculoskeletal anomalies	12	1.1				
24	Chondodystrophy and osteodystrophy	13	1.2				
25	Anomalies of diaphragm	27	2.5				
26	Anomalies of abdominal wall	25	2.3				
26a	Exomphalos	12	1.1				
26b	Gastroschisis	13	1.2				
27	Skin and other integument anomalies	30	2.8				
28	Non-chromosomal syndromes, presumed de-novo	29	2.7				
29	Multiply malformed cases	84	7.7				
30	Other sequences: Poland, Ivemark, Robin	12	1.1				

Note: underlined subgroups are those analysed in relation to distance from waste sites (section 4.2)

Siblings and twins

There were four sib-pairs amongst the cases: at distances of 3.3 km and 6.8 km in study area 13, 4.2 km in study area 12, and 6.8 km in study area 1. Sib pairs were included in the analyses as separate outcomes. In none of these sib pairs there was obvious familial transmission. Forty-two cases were reported to be twin births. These include 6 twin pairs where both twins were malformed and where both were treated as one case outcome.

4.2 RISK OF CONGENITAL ANOMALY IN RELATION TO DISTANCE OF RESIDENCE FROM LANDFILL SITES

This section describes the relationship between proximity to landfill sites and risk of congenital anomaly. The role of potential confounding factors, socio-economic status and maternal age, is evaluated in section 4.2.1, the risk of congenital anomaly in dichotomous distance bands in section 4.2.2, and the risk of congenital anomaly with continuous distance in section 4.2.3.

4.2.1 Potential confounding factors: socio-economic status and maternal age

In order to play a confounding role in the relationship between risk of congenital anomaly and distance of residence from landfill sites, socio-economic status and maternal age would need to be related to risk of congenital anomaly and to proximity to landfill sites. It is important to bear in mind that factors can play a confounding role even when such relationships do not reach statistical significance level.

In Table 4.5 the relationship between the two potential confounders measured in this study, maternal age and socio-economic status, and the risk of congenital malformations is shown. Maternal age analyses are pooled over all centres, socio-economic status is shown for each of the non-U.K. centres separately. The relationship between socio-economic status and risk of congenital anomaly in the U.K. centres is discussed in detail in section 4.5.

There was no evidence for a relationship between risk of non-chromosomal anomalies and maternal age (p for trend=0.85, Table 4.5). The risk of chromosomal anomalies was significantly higher in mothers between 30 and 34 years of age (OR 1.54, 95%CI 1.06-2.24) and mothers of 35 years and older (OR 5.36, 95%CI 3.66-7.86), than in younger mothers

(25-29 years as baseline), a relationship which is well-documented in the literature (Gaulden, 1992). The trend of increasing risk of chromosomal anomalies with increasing maternal age was of borderline statistical significance (p=0.06).

Table 4.5: Odds ratios for non-chromosomal and chromosomal anomalies by maternal age and socio-economic status

	controls	*non-chromosomal cases*			*trend test*	*chromosomal cases*			*trend test*
	*N***	*N*	*OR**	*95% CI*	*p-value*	*N*	*OR**	*95% CI*	*p-value*
Maternal age - all study areas pooled									
<20 years	184 (175)	73	1.03	0.76 - 1.40		16	1.12	0.62 - 2.01	
20-24 years	641 (615)	270	1.02	0.84 - 1.23		38	0.79	0.51 - 1.20	
25-29 years	889 (851)	391	1.00			65	1.00		
30-34 years	527 (492)	232	1.01	0.82 - 1.23		62	1.54	1.06 - 2.24	
>= 35 years	192 (158)	85	1.07	0.80 - 1.45	0.85	86	5.36	3.66 - 7.86	0.06
unknown	75 (75)	38				3			
Socio-economic status - non-UK centres									
Odense - social class									
1: high	5	2	1.01	0.17 - 5.89		0			
2	4	2	1.22	0.20 - 7.57		0	class 1 , 2, 3 combined		
3	33	13	1.00			6	1.00		
4	48	18	0.95	0.41 - 2.19		1	class 4,5 combined		
5: low	20	11	1.39	0.52 - 3.69	0.70	2	0.32	0.08 - 1.34	
unknown	1	2							
Lyon - maternal occupational									
professional	8	1	0.20	0.02 1.78		1			
intermediate	22	11	0.82	0.31 2.16		0			
farmers, craftsmen	7	4	0.98	0.24 3.97		0			
workmen	26	15	1.00			2			
unemployed	8	0	-		0.95	0			
unknown	4	7							
Antwerp - quintiles of average area income									
1: high income	45	25	1.75	0.81 - 3.79		5	2.95	0.53 - 16.52	
2	50	23	1.73	0.81 - 3.69		4	2.33	0.41 - 13.28	
3	58	15	1.00			2	1.00		
4	50	21	1.59	0.74 - 3.43		2	1.15	0.16 - 8.51	
5: low income	53	28	1.84	0.88 - 3.85	0.92	2	1.03	0.14 - 7.71	0.13
unknown	2	2							
Tuscany - maternal education									
1: graduate	15	8	0.58	0.23 - 1.45		3			
2: high school	67	77	1.20	0.76 - 1.90		7	class 1,2,3 combined		
3: medium	86	77	1.00			1	1.00		
4: elementary	56	29	0.60	0.35 - 1.04		5	class 4,5 combined		
5: none	1	1	1.23	0.08 - 20.02	0.17	0	0.77	0.27 - 2.16	
unknown	34	33							
Slovenia - maternal education									
1: university	8					1			
2: high school	6					8	class 1,2,3 combined		
3: vocational school	7					4	1.00		
4: secondary school	0					1	class 4, 5 combined		
5: primary school	8					1	0.81	0.12 - 5.49	

* adjusted for distance from waste site (0-3 km , 3-7km)

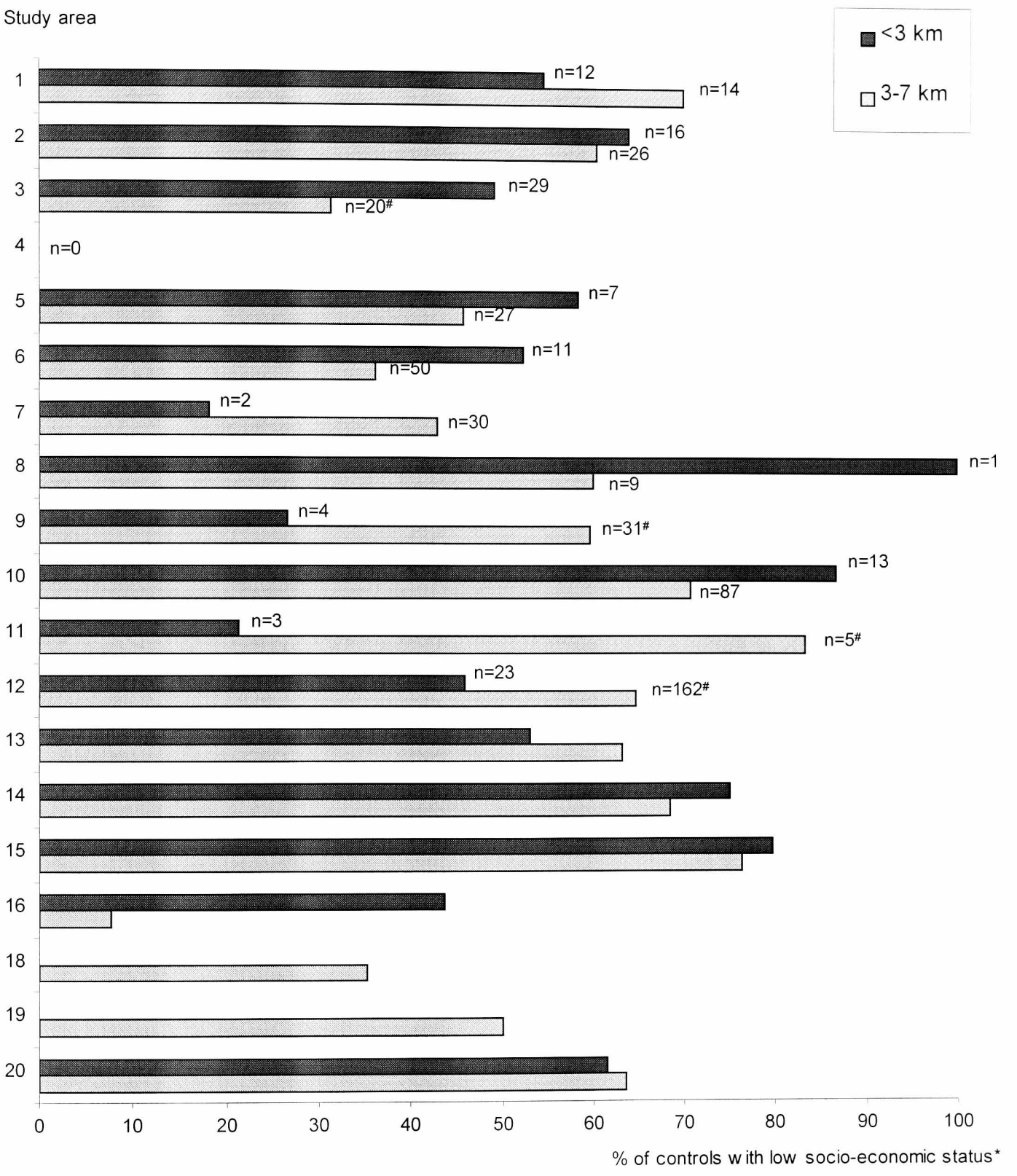
** in brackets: number of controls used for non-chromosomal analyses, not including data from Slovenia and England&Wales Down Syndrome Register study areas.

Whereas a statistically significant trend of increasing risk of non-chromosomal anomalies with increasing deprivation is found in the U.K. centres (section 4.5, Table 4.22), there was no clear evidence for such a trend in any of the non-U.K. centres (Table 4.5). Odds ratio estimates were highest in the lowest social classes (class 5 or workmen in Lyon) in all centres. None of these odds ratios were statistically significant, nor were the trends in odds ratios with social class. Numbers of cases in some social class groups were small.

Numbers of chromosomal cases were extremely small in social class groups. Therefore, the three highest social classes (1, 2, and 3) were combined and compared with the two lowest (4 and 5) in Odense, Tuscany, and Slovenia. In these three centres the odds ratio for chromosomal anomalies was lower in lower social classes (class 4 and 5 combined); none of the odds ratios were statistically significant (Odense OR 0.32, 95%CI 0.08-1.34; Tuscany OR 0.77, 95%CI 0.27-2.16; Slovenia OR 0.88, 95%CI 0.12-5.49) (Table 4.5). In Antwerp, odds ratios for chromosomal anomalies were higher in the highest income areas than in the low income areas. This trend was not statistically significant (p=0.13). The odds ratios in Table 4.5 have not been adjusted for maternal age.

Figure 4.1 shows the percentage of controls from lower social classes in 0-3 and 3-7 km distance zones in 19 EUROHAZCON study areas. In one area, study area 17 in Slovenia, information on socio-economic status was missing for all controls. In nine areas (2, 3, 5, 6, 8, 10, 14, 15, and 16) the percentage of controls from lower social classes was higher in the 0-3 km than in the 3-7 km zone, indicating that in these areas socio-economically deprived populations tended to live nearer the waste sites than more affluent populations. In two of these areas, areas 3 and 16, the difference between the two distance zones was statistically significant ($p<0.05$). In ten areas more deprived controls tended to live more frequently in the 3-7 km area than in the 0-3 km area. In four of these areas (9, 11, 12, and 13) the percentage of more deprived controls was statistically significantly higher in the 3-7 km zone. From Figure 4.1 it can be concluded that overall there was no consistent pattern of more deprived populations living closer to landfill sites. Indeed, for all study areas combined, the percentage of controls in lower social classes (defined according to Figure 4.2 footnote) was greater further away from sites (57% in the 3-7 km zone compared to 52% in 0-3 km zone). After stratification by study area this difference is not statistically significant ($MH\chi^2 = 2.7$, $p=0.09$).

Figure 4.1: Percentage of controls with low socio-economic status close by and further away from landfill sites in EUROHAZCON study areas

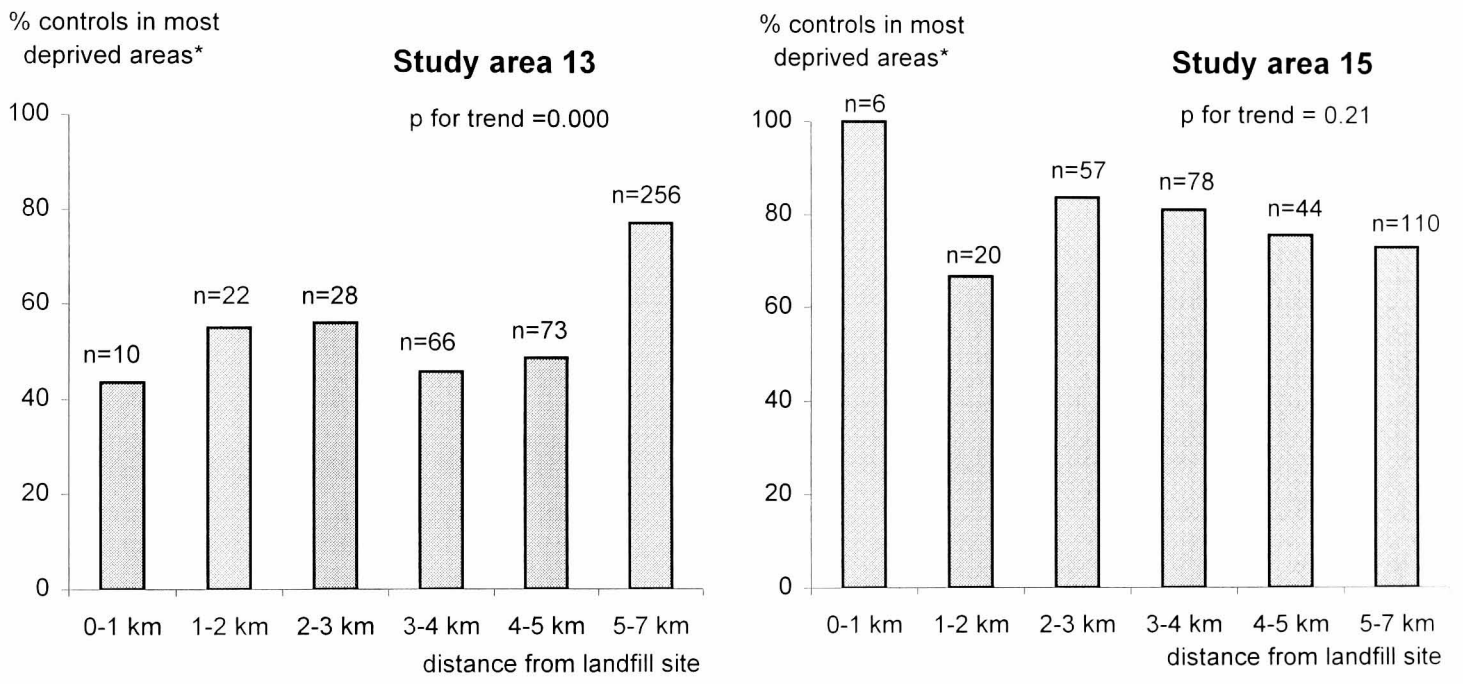


χ^2 p-value <0.05

* area 1, 2, and 5 : % with social class 4 or 5 (from parental occupation);
area 6, 7, 8: % in average area income quintiles 4 or 5 (lowest income areas);
area 9, 10, 11, 16: % with less then high school education (maternal education);
area 3, 4, 12-15, 18-20: % in UK small area deprivation quintiles 4 or 5 (most deprived areas).

In most study areas the numbers of controls were too small to look at the distribution of socio-economic status in more finely defined distance zones. Figure 4.2 shows this distribution for the two most densely populated study areas only, area 13 and 15 (accounting for 46% of all controls), in 6 distance bands. In area 13 more deprived populations tended to live further away from the site and this trend was statistically significant (χ^2 for trend=33.7, p=0.000). In area 15 a non-statistically significant trend of decreasing deprivation with increasing distance was found (χ^2 for trend =1.5, p=0.21). These findings agree with findings for dichotomous distance bands as shown in Figure 4.1.

Figure 4.2 : Percentage of controls with low socio-economic status by distance from landfill site in two EUROHAZCON study areas



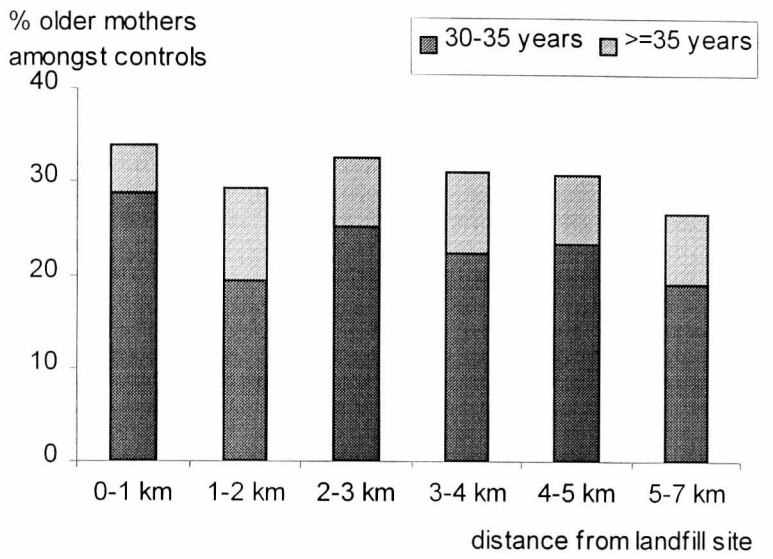
* % controls in deprivation quintiles 4 and 5

Figure 4.3 shows the percentage of older mothers by distance from landfill sites. The percentage of older mothers (>=30 years) declined with distance from the landfill sites in all study areas pooled, from 34% in the 0-1 km band to 27% in the 5-7 km band (χ^2 for trend=3.5, p=0.06), as shown in Figure 4.3. The percentage of mothers over the age of 35 did not show a relationship with distance of residence from landfill site.

Although the percentage of older mothers declined with continuous distance, there was little difference in the maternal age distribution between the 0-3 and 3-7 km bands in all study areas pooled: within 3 km of the landfill sites 68% of mothers was under 30 years of age, 24% between 30 and 34 years, and 8% 35 years or more; in the 3-7 km band these percentages were 71%, 21%, and 8% respectively (χ^2=1.79, df=2, p=0.41). In 6 out of 20 of

the separate study areas (areas 2, 4, 6, 9, 12, 13) the percentage of older mothers (>=30 years) was higher within 3 km than 3-7 km. In none of the study areas there was a statistically significant difference in the percentage of older mothers between the 0-3 and 3-7 km distance bands.

Figure 4.3: Percentage older mothers amongst controls by distance from landfill site - study areas 1-20 pooled



4.2.2 Risk of congenital anomaly in dichotomous distance zones

Table 4.6 presents the odds ratios for living within 3 km from a waste site compared to 3-7 km, for non-chromosomal congenital anomalies. Odds ratios are shown for each of the 15 study areas (containing 21 landfill sites) in which data on non-chromosomal anomalies were collected and for all these study areas combined, unadjusted and adjusted for socio-economic status and maternal age. The odds ratio for all study areas combined showed a statistically significant increase, both before and after adjustment (adjusted OR 1.33; 95% CI 1.11-1.59). Adjustment for socio-economic status and maternal age did not change the odds ratio substantially: adjustment led to a change from 1.37 to 1.33 in the odds ratio estimate.

Adjusted odds ratios for study areas 7, 13, and 15 showed a statistically significant increase with odds ratio estimates of 3.93 (95% CI 1.20-12.80), 1.50 (95% CI 1.05-2.13) and 1.63 (95% CI 1.09-2.44) respectively. In study area 6 the odds ratio bordered statistical significance after adjustment (OR 2.08; 95% CI 0.98-4.41). In the majority of individual areas adjustment for confounding factors resulted in bringing the odds ratio estimates closer to unity. The effect of adjustment was generally small however, not changing the odds ratios substantially.

Although odds ratios for individual study areas varied between 0 and 2.92 (unadjusted) there was little evidence for heterogeneity in the odds ratios between sites. The p-value for the interaction between study area and distance from landfill site was 0.31. As discussed in section 3.7.1.2 this test for heterogeneity may not be very powerful and the strength of the association may be overestimated in the fixed model. Random effects models applied to the data did not suggest different interpretations of the association. Odds ratio estimates and confidence intervals were generally within 0.02 of those estimated in the fixed model. The most usual Bayes model gave an odds ratio distributed around 1.35, with 95% 'credible interval' 1.07-1.68 and p-value 0.007: still substantial evidence for an association.

Table 4.6: Odds ratios for living within 3 km from a hazardous waste landfill site - non-chromosomal anomalies

	distance band	*cases*	*controls*	*OR*	*95%CI*	*adj. OR*	*95%CI*
Study area 1-15 pooled:							
	0-3 km	295	511	1.37	1.14 - 1.63	1.33	1.11 - 1.59
	3-7 km	794	1855				
Study area							
1	0-3 km	7	23	0.49	0.15 - 1.63	0.43	0.11 - 1.65
	3-7 km	12	21				
2	0-3 km	11	25	1.26	0.47 - 3.40	1.23	0.41 - 3.67
	3-7 km	17	43				
3	0-3 km	25	59	1.16	0.60 - 2.26	0.76	0.34 - 1.69
	3-7 km	25	65				
4	0-3 km	6	18	1.12	0.19 - 6.42	0.83	0.11 - 6.07
	3-7 km	4	12				
5	0-3 km	4	14	0.58	0.17 - 1.91	0.45	0.13 - 1.60
	3-7 km	31	64				
6	0-3 km	18	21	2.19	1.08 - 4.45	2.08	0.98 - 4.41
	3-7 km	55	139				
7	0-3 km	11	11	2.92	1.11 - 7.70	3.93	1.20 - 12.80
	3-7 km	24	71				
8	0-3 km	0	1	0.00		-	
	3-7 km	6	15				
9	0-3 km	21	15	2.09	0.92 - 4.75	1.29	0.48 - 3.49
	3-7 km	39	52				
10	0-3 km	17	15	1.38	0.65 - 2.94	1.40	0.62 - 3.15
	3-7 km	104	123				
11	0-3 km	28	38	0.65	0.28 - 1.52	0.72	0.17 - 2.97
	3-7 km	17	15				
12	0-3 km	23	50	1.16	0.67 - 2.02	1.26	0.71 - 2.22
	3-7 km	97	250				
13	0-3 km	64	113	1.52	1.08 - 2.15	1.50	1.05 - 2.13
	3-7 km	232	627				
14	0-3 km	1	4	0.63	0.07 - 6.16	0.94	0.09 - 9.74
	3-7 km	22	54				
15	0-3 km	59	104	1.58	1.07 - 2.33	1.63	1.09 - 2.44
	3-7 km	109	304				

* adjusted for socioeconomic status and maternal age

Table 4.7: Odds ratios for living within 3 km from a hazardous waste landfill site - chromosomal anomalies

	distance band	*cases*	*controls*	*OR*	*95%CI*	*adj. OR**	*95%CI*
Study area 1-20 pooled							
	< 3km	74	557	1.18	0.87 - 1.62	1.29	0.79 - 2.10
	3-7 km	196	1951				
Study area 1-15 pooled							
	< 3km	56	511	1.33	0.94 - 1.89	1.41	0.97 - 2.04
	3-7 km	148	1855				
Study area							
1	< 3 km	2	23	1.83	0.15 - 21.64	2.53	0.16 - 40.09
	3-7 km	1	21				
2	< 3 km	3	25	1.72	0.32 - 9.18	1.32	0.20 - 8.80
	3-7 km	3	43				
3	0-3 km	4	59	0.55	0.16 - 1.92	0.76	0.17 - 3.28
	3-7 km	8	65				
4	0-3 km	3	18	1.00	0.15 - 6.91	1.00	0.11 - 8.79
	3-7 km	2	12				
5	0-3 km	0	14	0.00		-	
	3-7 km	4	64				
6	0-3 km	2	21	2.65	0.48 - 14.53	2.73	0.49 - 15.19
	3-7 km	5	139				
7	0-3 km	1	11	1.29	0.14 - 12.11	2.33	0.21 - 26.15
	3-7 km	5	71				
8	0-3 km	0	1	0.00		-	
	3-7 km	2	15				
9	0-3 km	2	15	1.39	0.24 - 7.88	1.07	0.17 - 6.81
	3-7 km	5	52				
10	0-3 km	4	15	2.52	0.73 - 8.74	3.89	0.98 - 15.46
	3-7 km	13	123				
11	0-3 km	4	38	0.40	0.09 - 1.79	0.35	0.06 - 1.98
	3-7 km	4	15				
12	0-3 km	6	50	1.36	0.53 - 3.53	1.30	0.48 - 3.54
	3-7 km	22	250				
13	0-3 km	14	113	1.59	0.85 - 2.97	1.50	0.78 - 2.90
	3-7 km	49	627				
14	0-3 km	0	4	0.00		-	
	3-7 km	6	54				
15	0-3 km	11	104	1.69	0.78 - 3.67	1.77	0.80 - 3.88
	3-7 km	19	304				
16**	0-3 km	3	16	0.22	0.05 - 0.94	0.23	0.05 - 1.12
	3-7 km	12	14				
17**	0-3 km	1	1	2.33	0.11 - 50.98	-	
	3-7 km	3	7				
18**	0-3 km	1	1	2.13	0.12 - 38.48	1.98	0.06 - 62.49
	3-7 km	8	17				
19**	0-3 km	4	2	7.00	0.92 - 53.23	17.69	1.15 - 273.30
	3-7 km	4	14				
20**	0-3 km	9	26	0.73	0.29 - 1.82	0.75	0.28 - 1.95
	3-7 km	21	44				

* pooled ORs adjusted for socio-economic status and maternal age; ORs in individual study areas adjusted for maternal age.

** Down Syndrome only

In Table 4.7 odds ratios for living within 3 km of a landfill site are presented for chromosomal anomalies. Odds ratios were calculated both for all 20 study areas combined and for study areas 1 to 15 combined. The latter are the same study areas for which non-chromosomal analyses had been carried out. The adjusted odds ratio for all 20 study areas combined was 1.29 and did not reach statistical significance (95% CI 0.79-2.10). The odds ratio for study areas 1-15 combined showed an increase of borderline statistical significance after adjustment for confounding factors (OR 1.41; 95%CI 0.97-2.04). Adjustment for confounding factors increased the odds ratio estimates (from 1.18 to 1.29 for study area 1-20, from 1.33 to 1.41 for study area 1-15). This effect was mainly due to adjustment for maternal age.

In most individual study areas odds ratios for chromosomal anomalies did not reach statistical significance before or after adjustment for maternal age. Odds ratios in individual study areas were adjusted for maternal age only, not for socio-economic status, since adjustments for both factors led to very unstable logistic regression models in many cases due to small numbers. In study area 16 a statistically significant deficit of cases is found in the 0-3 km zone before maternal age adjustment (OR 0.22, 95% CI 0.05-0.94). After adjustment this odds ratio no longer reached statistical significance. Results for study areas 16 and 17 should be interpreted with caution since terminations of pregnancy were not included in the data which may have led to bias. Area 19 showed a large, and statistically significant excess of cases in the 0-3 km zone. The adjusted odds ratio is 17.7 and has a very wide confidence interval (1.15-273.3). In this area there were 3 cases with the same postcode within 3 km of the waste site. These cases were compared for their exact address, date of birth, and the age of the mother but there was no evidence that these cases were duplicates or siblings.

There was little evidence for heterogeneity in the odds ratios between study areas 1 to 20 (p for heterogeneity=0.57) or between study areas 1 to 15 (p for heterogeneity=0.94). Random effects models were not fitted to data for chromosomal anomalies.

Table 4.8 presents the odds ratios for living within 3 km of a landfill site compared to 3-7 km for selected malformation subgroups, combining data from 15 study areas for all anomaly groups and 20 study areas for Down Syndrome. In some subgroups with few cases only unadjusted odds ratios could be calculated when logistic regression models incorporating confounding factors were very unstable. In larger subgroups both unadjusted and adjusted odds ratios are shown in Table 4.8. Adjustment for confounding factors did not change the odds ratios substantially in these subgroups. Most malformation subgroups showed raised odds ratios although in few was the increase statistically significant. Numbers of cases were

small in most subgroups and thus confidence intervals were wide. Odds ratios for neural tube defects (adj OR 1.88; 95% CI 1.24-2.83), malformations of the cardiac septa (adj OR 1.45; 95% CI 1.05-2.00), and anomalies of the great arteries and veins (adj OR 1.88; 95% CI 1.05-3.38) were statistically significant. Tracheo-oesophageal anomalies, hypospadias, and gastroschisis showed odds ratios (unadjusted) of borderline statistical significance. The odds ratios were 2.25 (95% CI 0.96-5.26), 1.96 (95% CI 0.98-3.92), and 3.19 (0.95-10.77) respectively.

Table 4.8: Odds ratios for living within 3 km from a hazardous waste landfill site - selected malformation subgroups

malformation subgroup		*N*	*OR*	*95% CI*	*adj OR**	*95% CI*
NON-CHROMOSOMAL ANOMALIES						
1	neural tube defects	130	1.86	1.24 - 2.79	1.88	1.24 - 2.83
2	hydrocephaly	32	1.06	0.44 - 2.59		
3+4	other central nervous system defects	23	1.03	0.36 - 2.94	0.82	1.20 - 0.57
7	malformations of cardiac chambers and connections	45	0.91	0.42 - 1.97	1.01	0.46 - 2.22
8	malformations of cardiac septa	248	1.49	1.09 - 2.04	1.45	1.05 - 2.00
9	malformations of valves and other heart malformations	109	1.17	0.73 - 1.88	1.20	0.73 - 1.95
10a	anomalies of great arteries and veins	63	1.81	1.02 - 3.20	1.88	1.05 - 3.38
13a	cleft palate	38	1.63	0.77 - 3.41	1.56	0.74 - 3.30
13b	cleft lip with or without cleft palate	72	1.18	0.66 - 2.12	1.11	0.62 - 2.02
14	tracheo-oesophageal fistula, oesophageal atresia and stenosis	25	2.25	0.96 - 5.26		
15	digestive system and upper alimentary tract	59	0.98	0.49 - 1.93	0.93	0.46 - 1.89
16	atresia and stenosis of rectum and anal canal	20	1.02	0.33 - 3.15		
17	hypospadias	45	1.96	0.98 - 3.92	1.93	0.96 - 3.91
19	renal anomalies	75	1.30	0.73 - 2.31	1.46	0.81 - 2.63
20	urinary tract anomalies	69	1.14	0.62 - 2.11	1.24	0.66 - 2.34
21	limb reduction defects	41	1.27	0.61 - 2.62	1.10	0.52 - 2.31
25	anomalies of diapraghm	27	1.10	0.42 - 2.87	1.07	0.39 - 2.95
26a	exomphalos	12	0.26	0.03 - 2.19	0.36	0.04 - 3.03
26b	gastroschisis	13	3.19	0.95 - 10.77		
27	skin and other integument anomalies	30	1.92	0.78 - 4.73	1.60	0.64 - 4.01
28	syndromes, presumed de-novo mutations	29	1.48	0.63 - 3.49		
29	multiply malformed cases	84	1.21	0.71 - 2.06	1.22	0.71 - 2.11
CHROMOSOMAL ANOMALIES						
31a	Down Syndrome					
	- study area 1-20	195	1.12	0.78 - 1.61	1.18	0.86 - 1.62
	- study area 1-15	129	1.32	0.86 - 2.03	1.31	0.83 - 2.07
31b	Non Down Syndrome chromosomal					
	- study area 1-15	75	1.37	0.78 - 2.42	1.50	0.82 - 2.74

* adjusted for maternal age and socio-economic status

4.2.3 Risk of congenital anomaly with continuous distance

Table 4.9 shows odds ratios for non-chromosomal anomalies in six distance bands, and several models fitting distance as a continuous variable. Over the six distance bands a fairly consistent decrease in risk with distance is seen. All models fitting distance as a continuous variable showed a statistically significant decreasing risk with distance from site ($p<0.05$). Model *3* in Table 4.9, fitting an exponential decline of excess risk (odds ratio) with distance, fitted the data slightly better than logistic regression models of distance (model *1*) and the reciprocal of distance (model *2*), or the exponential excess model fitting distance squared (model *4*). From model *3* an odds ratio right next to site (α) compared to far away of 2.18 (95% CI 1.38-3.51) was estimated. Figure 4.4a graphically shows the decline in risk with distance as estimated through model *3*, and the odds ratio estimates in the six distance bands. Figure 4.4b shows the decline in risk with distance estimated from model *4*.

Table 4.9: Risk of non-chromosomal anomaly with distance of residence from landfill sites - study area 1-15 pooled

Model						*df*	*Deviance*	*p (model)*
Distance (d) in 6 bands								
d (km)	*cases*	*controls*		*OR**	*95%CI*			
<=1	41	62		1.60	1.03 - 2.48			
1-2	84	167		1.25	0.92 - 1.70			
2-3	170	282		1.46	1.15 - 1.85			
3-4	236	478		1.17	0.95 - 1.44			
4-5	206	469		1.06	0.86 - 1.32			
5-7	352	908		1.00		5	4199.8	0.025
Logistic regression model:*								
1) exp(β*d)			β=	-0.08		1	4202.2	0.001
2) exp(β*1/d)			β=	0.32		1	4206.5	0.012
Exponential excess risk model:*					95%CI			
3) {1 + α*exp(-γ*d)}			α=	1.18	0.38 - 2.51**	2	4201.7	0.004
			γ=	-0.28				
4) {1 + α*exp(-γ*d^2)}			α=	0.55	0.21 - 1.79**	2	4202.9	0.007
			γ=	-0.033				
*Null model**						0	4212.7	

* adjusted for maternal age and socio-economic status

** 95% CI estimated keeping γ fixed

Chromosomal anomalies did not show a decline in risk with distance either when analysing risk in six distance bands or when modelling distance as a continuous variable (Table 4.10). Table 4.10 shows results for all 20 study areas combined. Results were essentially the same when pooled data for study areas 1-15 were analysed (Table 4.11).

Figure 4.4 : Risk of non-chromosomal anomaly with of residence distance from landfill sites

Note: Line shows ORs fitted by exponential excess risk model with hypothetical risk infinitely far from site as baseline (lefthand scale); diamonds and error bars show ORs and 95% CI for 6 distance bands with 5-7 km as baseline (righthand scale). Different scales are needed because baselines differ : at 6 km the exponential excess line indicates a risk of 1.22 (in Figure 4.4a) and 1.16 (in Figure 4.4b) relative to risk infinitely far from the site; the diamond at this point represents the 5-7 km baseline.

Figure 4.4a: Exponential excess model 1: {1 + α*exp(-γ*d)}

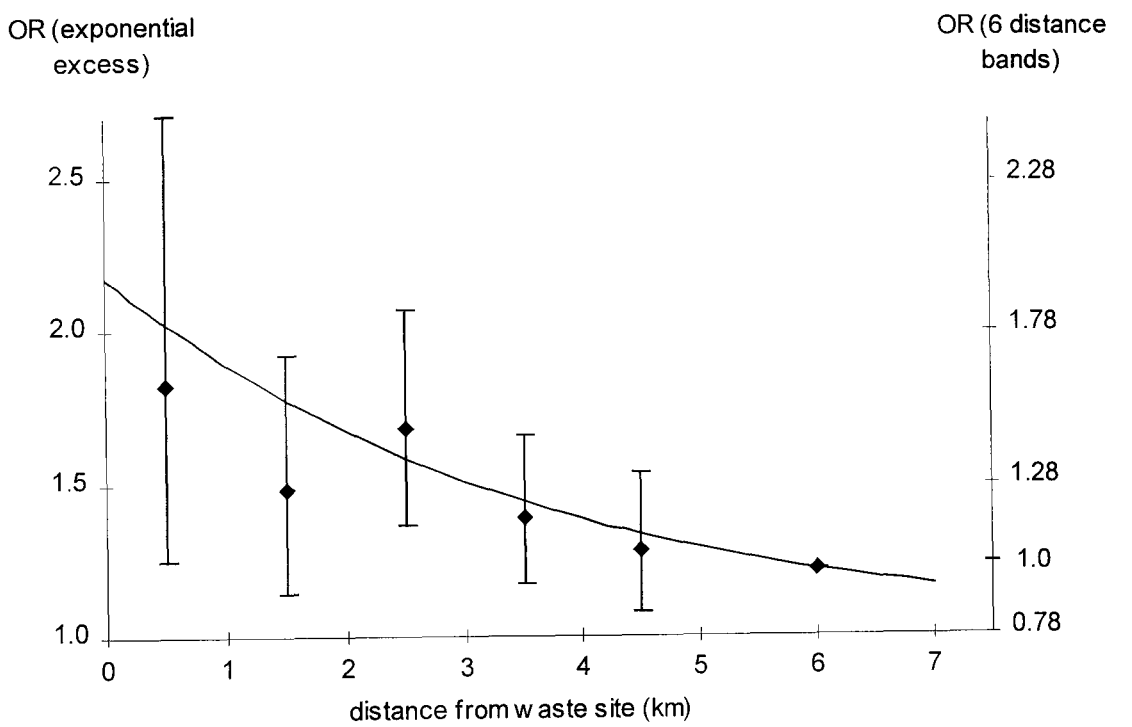


Figure 4.4b: Exponential excess model 2: {1 + α*exp(-γ*d^2)}

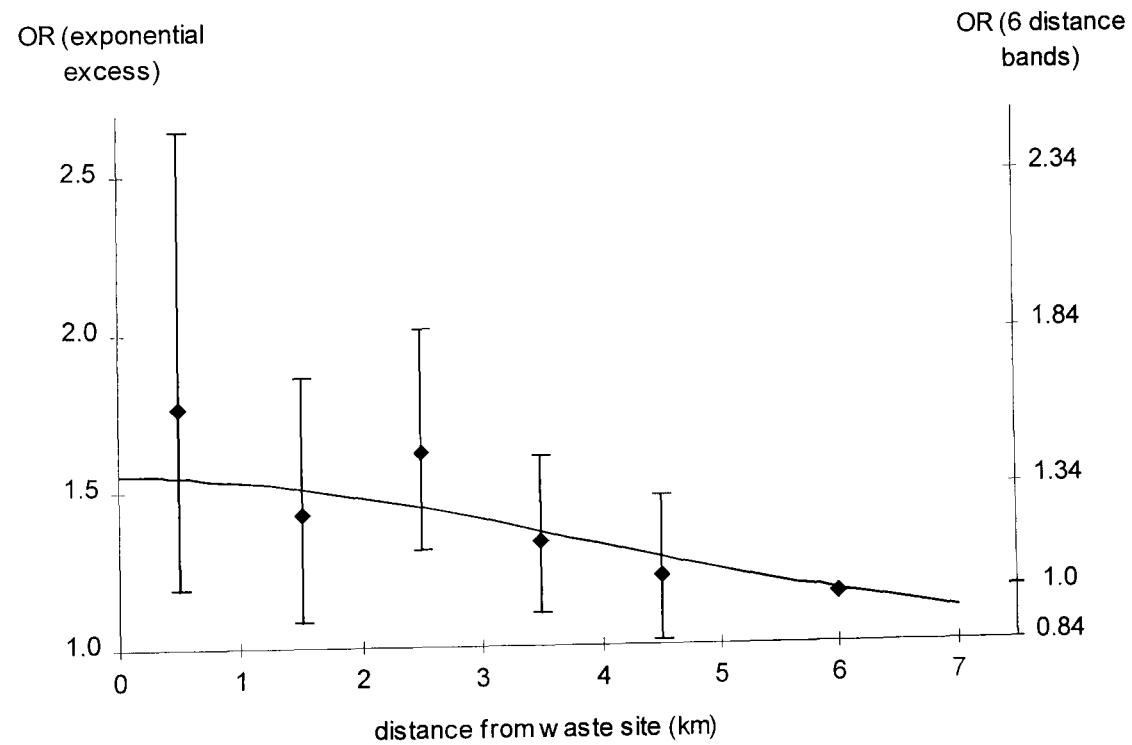


Table 4.10: Risk of chromosomal anomaly with distance of residence from landfill sites – study areas 1-20 pooled

Model					*df*	*Deviance*	*p (model)*
Distance (d) in 6 bands							
d (km)	*cases*	*controls*	*OR**	*95%CI*			
<=1	8	63	1.52	0.66 - 3.46			
1-2	20	184	1.00	0.57 - 1.74			
2-3	46	310	1.49	0.99 - 2.26			
3-4	53	512	0.98	0.67 - 1.45			
4-5	50	489	1.16	0.78 - 1.71			
5-7	93	950	1.00		5	1562.0	p=0.41
Logistic regression model:*							
1) exp(β*d)			β= -0.028		1	1566.6	p=0.52
2) exp(β*1/d)			β= 0.132		1	1566.8	p=0.61
Exponential excess risk model:*							
3) {1 + α*exp(-γ*d)}			α= 0.36		2	1566.5	p=0.76
			γ= -0.33				
4) {1 + α*exp(-γ*d^2)}			α= 0.85		2	1566.9	p=0.95
			γ= -0.001				
*Null model**					0	1567.0	

* adjusted for maternal age

Table 4.11: Risk of chromosomal anomaly with distance of residence from landfill sites – study areas 1-15 pooled

Model					*df*	*Deviance*	*p (model)*
Distance (d) in 6 bands							
d (km)	*cases*	*controls*	*OR**	*95%CI*			
<=1	8	62	1.74	0.75 - 4.04			
1-2	16	167	1.22	0.66 - 2.26			
2-3	32	282	1.58	0.98 - 2.54			
3-4	39	478	1.03	0.66 - 1.59			
4-5	42	469	1.21	0.79 - 1.86			
5-7	67	908	1.00		5	1287.1	p=0.44
Logistic regression model:*							
1) exp(β*d)			β= -0.065		1	1290.1	p=0.17
2) exp(β*1/d)			β= 0.296		1	1290.7	p=0.27
Exponential excess risk model:*							
3) {1 + α*exp(-γ*d)}			α= 0.92		2	1289.8	p=0.34
			γ= -0.40				
4) {1 + α*exp(-γ*d^2)}			α= 0.55		2	1289.7	p=0.32
			γ= -0.104				
*Null model**					0	1291.9	

* adjusted for maternal age

4.3 HAZARD SCORING OF EUROHAZCON STUDY SITES

This section presents results of the landfill ranking questionnaire, including questionnaire response and detailed site descriptions, as well as results of the experts panel scoring of the landfill sites including initial and final expert hazard scores, agreement between experts, and the final hazard potential classification of study sites to be used in analyses of the relationship between hazard potential and risk of congenital anomaly near sites (section 4.4).

The landfill ranking questionnaire was completed for 25 EUROHAZCON study sites, not for the three sites (sites 18, 19, 20) selected in study regions of the England & Wales Down Syndrome Register (section 3.6.2.2). Two sites in North East Italy for which questionnaires were completed were later excluded from all analyses (see also section 3.2). Questionnaires for the two Slovenian sites (sites 16 and 17) were completed but not included in the hazard classification in order to keep classifications of sites the same in analyses of both non-chromosomal and chromosomal anomalies. All results described in this section (4.3) and the following (4.4) are based therefore on the 21 study sites (in 15 study areas) for which questionnaires were completed and data on both non-chromosomal and chromosomal anomalies were collected, not including sites in North-East Italy, Slovenia, and the England & Wales Down Syndrome Register. These 21 study sites and 15 study areas are the same as those on which the analyses of non-chromosomal anomalies in previous sections were based (section 4.2.2 and 4.2.3).

4.3.1 Landfill questionnaire results

The landfill questionnaire gave reasonably complete information on age and size of the EUROHAZCON study sites, soil type, and engineering and monitoring practices. Response rates for these items varied between 86 and 100% (Table 4.12). Items related to whether off-site migration of substances from the landfill had occurred in ground or surface water or whether off-site migration of landfill gas had occurred were least well completed (43-57% response).

Table 4.12: Landfill Site Ranking Questionnaire response

Questionnaire items	*Response**	
	N	*%*
Total site area	21	100%
Total quantity of waste in place: volume or weight, depth	19	90%
Hazardous waste' quantity or % of total waste classified as 'hazardous'	12	57%
Types of hazardous and industrial waste deposited	18	86%
Containment / lining	21	100%
Covering	21	100%
Capping	21	100%
Leachate collection system	21	100%
Leachate monitoring	21	100%
Soil Type and permeability	21	100%
Groundwater depth	15	71%
Groundwater monitoring	21	100%
Groundwater contamination	12	57%
Public drinking water supply extraction points within 3 km	18	86%
Private water supply extraction points within 3 km	18	86%
Surface water: type and distance	20	95%
Surface water monitoring	21	100%
Surface water contamination	9	43%
Landfill gas control system	18	86%
Landfill gas monitoring	18	86%
Landfill gas migration	9	43%
Complaints about smells and odours from the landfill	11	52%
Rainfall	16	76%
Landuse for recreation and/or food consumption within 3 km	19	90%

* number and percentage of sites for which information on each questionnaire item was obtained

For the majority of sites some monitoring results of either leachate, ground water, surface water, or landfill gas were available but this type of information was not easily comparable between sites; monitoring was carried out for different substances, with different frequencies, on- and off-site, and in different years either during the study period or before. Routine monitoring was most common for groundwater and landfill gas (Table 4.13). At six sites no routine monitoring took place although at four of these some incidental site investigations had been carried out in the past. At only one site were all four media (leachate, groundwater, surface water and landfill gas) monitored. At two sites both groundwater and landfill gas, the most important potential pathways of off-site migration, were routinely monitored. Summary reports of site investigations and monitoring were available for only six sites.

Table 4.13 : Frequency of monitoring of environmental media at study sites

	Number of sites with monitoring:			
	routine	*incidental*	*none*	*not known*
leachate	5	8	8	
groundwater	9	5	7	
surface water	6	2	13	
landfill gas	8	4	6*	3

* at 4 of these sites reportedly no biodegradable waste present

Sites had all been reported to contain hazardous waste (as defined through the EC directive), but the amount of detail in the information collected through the questionnaire on exact types and quantities of wastes was very variable (Table 4.14). In most cases information on 'hazardous' wastes deposited was limited to the types of industries from which the wastes originated.

Table 4.14: Types of 'hazardous' waste deposited – information obtained from the Landfill Site Ranking Questionnaire

Site	*Types of industrial and/or 'hazardous' waste the site took or was licensed to take*
1	Tannery wastes with primarily ammonium and chromium compounds, tarry residues, oils, halogenated solvents
2	Chlorinated solvents, tar, phenols, cyanide, organic solvents
3	Special and industrial wastes including oils, acids, alkalis, effluent/contaminated water and sludges, paint, leather industry wastes, phosphates, pesticides, electroplating wastes
4	Liquid wastes: cutting oils, alkali cleaners, detergents, unspecified hazardous liquids. Solid wastes including metal wastes, boiler ash, leather industry wastes
5	Various industrial toxic wastes including heavy metals, water treatment sludges, solvents: adhesives, varnishes, painting wastes
6	Unspecified industrial wastes
7a	Industrial wastes: radium, residues from copper production
7b	Copper production wastes
7c	Unspecified industrial wastes, chemical wastes, industrial water treatment sludges
8	Industrial wastes including paint, rubber, ink, leather, tar, and glue wastes, metal compounds, sludges with toxic metal compounds
9	Waste from ceramics and battery industry. Heavy metals (lead selenium), other, unspecified, hazardous industrial wastes
10	Incinerator waste, fly-ash, and contaminated soil/sludges, heavy metals (lead), solvents (tetrachloroethylene)
11	Heavy metals: lead, copper, zinc, arsenic. Wastes from production of sulphuric acid
12	Special and restricted waste. Licensed to take asbestos, organic residues, polymeric materials, tarry wastes, mixed laboratory chemicals, toxic solid materials including those containing biocides, paint wastes, ink, varnishes, glues, insoluble toxic metal salts, alkyl and non-alkyl mercury wastes, cyanide, arsenic, antimony, selenium
13a	Licensed to take inorganic and organic acids, alkalis, toxic metal compounds, miscellaneous chemical waste, treatment sludge, printing waste, tars, dyes, paints.
13b	Licensed to take long list of special wastes including toxic metal compounds, cadmium, lead, mercury, adhesives, paint, tar, glue, printing waste, miscellaneous chemical waste
13c	Unspecified industrial and special wastes
13d	Licensed to take industrial and special wastes including asbestos, boiler and flue cleaning, polymerisation products, adhesives, glue, and rubber wastes, mercury wastes
14	Licensed to take alkali metal oxides/hydroxides, metal waste, asbestos, boiler and flue cleanings, mineral processing wastes, polymeric products, paint wastes
15a	Special wastes have included asbestos; heavy metals; contaminated soils; cyanides; liquids and sludges: industrial treatment sludges (with nickel and chromium), acid wastes, alkali wastes, waste oils, paint washings and solvents, tannery and sewage sludge
15b	Waste from chemical works and chromium processing industry. Chromium III and VI, arsenic, lead

Information from the questionnaire on site engineering showed that most sites (14) did not have an engineered liner and can therefore be classified as 'dilute and disperse' sites. A leachate collection system was present at six sites, at two of these sites the collection

system was in place since the start of site operations. At four sites a gas collection system had been in place during at least part of the study period, one of which had been in operation since the start of the study period.

Questions about pollution incidents showed that groundwater contamination had been reported at seven of the study sites, related to organic solvents (2 sites), heavy metals (2 sites), and/or unspecified contaminants. At two sites volatile organic compounds had been measured in off-site air, one of these sites was also associated with serious surface water pollution. One site reported high chromium concentrations in soil on-site and groundwater, and low concentrations of chromium in the air. Other sites may have also have caused off-site contamination but when questionnaire questions were not completed and no summary reports of site investigations and/or routine monitoring were available, it was not possible to determine whether this was the case. At seven sites nearby residents had at some stage since the start of operations complained about smells from the sites.

4.3.2 Expert panel scoring

Initial scores assigned to the EUROHAZCON study sites by the expert panel are shown in Table 4.15. Hardly any sites were given the score of 1 (low hazard), with the exception of three sites for air hazard. Air hazard was generally scored lower than water hazard. Experts were not specifically asked to apply the full range of possible scores to the sites. As a result, one expert (expert 4) used a very limited range of scores, assigning mostly 3s and 4s to sites, whereas the other experts used a wider range of scores.

The agreement between experts as measured by the intra-class correlation coefficient, was better for overall and water hazard scores (ICC=0.52 for both) than for air hazard (ICC=0.21) (Table 4.15). The differences between the lowest and the highest expert score given to a site also reflect this. For the majority of sites the difference between expert scores is one point or less in the overall (17 sites) and water scoring (13 sites) whereas in the air scoring only eight sites show one point or less difference between experts (Table 4.16). Three sites show a difference of three points or more in the air hazard scoring.

Table 4.15: Initial expert panel hazard scores – individual scores and agreement between experts

	OVERALL				*WATER*				*AIR*			
	Expert				*Expert*				*Expert*			
site	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*
1	5	4	2.5	4	5	5	2.5	4	5	4	1	3
2	5	5	3.5	3	5	5	4	4	4	5	1.5	3
3	2	3	3	3	3	3	3	3	2	3	3.5	3
4	5	4.5	5	4	5	5	5	4	4	4	4.5	3
5	4	4.5	5	4	3	4	5	4	4	5	5	4
6	4	4	4.5	4	4	4	4.5	4	4	3	4.5	3
7a	2	3	4.5	3	4	4	4.5	3	2	2	3.5	3
7b	3	2	2	3	4	3	1.5	3	3	2	1	3
7c	3	3	3	4	4	4	3	4	3	2	3	3
8	4	4	4	4	5	4.5	4	4	4	4	4.5	3
9	3	3	3	4	3	4	3	4	2	2	3	3
10	3	3	3.5	3	3	4	3.5	3	3	2	3	3
11	4	3	3	4	3	3	3	4	4	2	2	3
12	4	3	3.5	3	4	2	4	3	4	3	2	2
13a	2	3	3.5	3	2	2	3.5	4	3	3	2.5	3
13b	3	4	3.5	3	4	4.5	4	3	3	3	3	3
13c	2	2	3	3	2	1.5	3	3	2	2.5	3	3
13d	2	3	3	3	2	2	3	3	2	3	3	4
14	2	2	3	3	2	2	2	2	2	2	3	3
15a	4	5	4.5	4	4	5	4.5	4	3	5	4.5	4
15b	4	4	4	4	4	5	4	4	1	2	4	3
ICC[#]	0.52				0.52				0.21			

[#] : intra-class correlation coefficient or inter-rater agreement, see section 3.3.2.1

Notes:
- although experts were asked to score from 1 to 5 in whole numbers, some gave in-between scores such as 1.5, 2.5, etc.
- underlined scores were later changed during the expert panel meeting
- although not explicitly asked to score overall hazard within the range of water and air scores, all experts did so with one slight exception: site 7a was scored 1-to-2 for water, 1 for air, and 2 for overall by one expert.

Table 4.16: Initial expert panel hazard scores – difference between highest and lowest expert score assigned to a site

difference in score:	*OVERALL number of sites:*	*WATER*	*AIR*
0	2	2	1
0.5	2	1	1
1	13	10	6
1.5	1	3	5
2	1	3	5
2.5	2	2	0
3	0	0	1
3.5	0	0	1
4	0	0	1
total	21	21	21

As discussed in section 3.6.2.2 experts were given the opportunity to change initial scores during an expert panel meeting. Scores that were changed are underlined in Table 4.15 (initial scores) and Table 4.17 (final scores). Few scores were changed in the overall and water hazard scoring: six and eight respectively. Differences between experts were greater for the air hazard scoring (see above) and 19 air scores for 12 sites were changed. Initial and final scores were very highly correlated for overall (correlation coefficient = 0.96), water (0.97), and air (0.93).

Table 4.17 shows the final scores experts gave to the 21 study sites. As expected, changes made at the expert panel meeting improved agreement between experts. The intra-class correlation coefficient (ICC) for overall and water hazard scores increased from 0.52 to 0.61 and 0.62 respectively. Agreement in air hazard scores increased substantially, with an increase in the ICC from 0.21 to 0.53, but is still lower than overall and water. Differences in the highest and lowest expert score given to a site show that the number of sites differing by 1 point or less is 19 in the final overall hazard scoring, 16 in the final water hazard scoring, and 15 in the final air hazard scoring (Table 4.18). Differences of two or more points are found for site 5 and 7b in the water score, and sites 1, 2, 7b, and 11 in the air score. The difference between the lowest and highest scoring expert is never more than 2.5 points in the final scores.

The final hazard score of each site was calculated as the average of the final scores of the four experts (Table 4.17). The reliability of the average score of the four experts was high for overall (ICC_k=0.86), water (ICC_k=0.86), and air hazard scores (ICC_k=0.82). Average scores covered a limited range with overall scores ranging from 2.50 to 4.63, water scores from 2.0 to 4.75, and air scores from 2.25 to 4.50. The average final overall and water scores were highly correlated, with a correlation coefficient of 0.87. Correlations between overall and air (0.76) and water and air (0.61) were not as strong. All correlation coefficients were statistically significant ($p<0.01$).

Tertiles of the final hazard scores were used to categorise study areas into those containing low, medium, and high hazard sites. Table 4.17 shows the hazard categories each site was assigned to. Each hazard category contains 5 study areas.

Table 4.17 : Final expert panel hazard scores - individual scores, average scores, hazard categories, and agreement between experts.

study area	site	OVERALL Expert 1	2	3	4	hazard score (average)	hazard category	WATER Expert 1	2	3	4	hazard score (average)	hazard category	AIR Expert 1	2	3	4	hazard score (average)	hazard category
1	1	3	4	2.5	4	3.38	medium	3	4	2.5	4	3.38	low	3	3	1	3	2.50	low
2	2	4	4	3.5	3	3.63	medium	5	5	4	4	4.50	high	4	5	3	3	3.75	high
3	3	2	3	3	3	2.75	low	3	3	3	3	3.00	low	3	3	3	3	3.00	medium
4	4	5	4.5	5	4	4.63	high	5	5	5	4	4.75	high	4	4	4.5	4	4.13	high
5	5	4	4.5	5	4	4.38	high	3	4	5	4	4.00	medium	4	5	5	4	4.50	high
6	6	4	4	4.5	4	4.13	high	4	4	4.5	4	4.13	high	4	3	4.5	3	3.63	high
7	7a	3	3	4.5	3	3.38		4	4	4.5	3	3.88		3	2	3.5	3	2.88	
	7b	3	2	2	3	2.50		4	3	1.5	3	2.88		3	2	1	3	2.25	
	7c	3	3	3	4	3.25		4	4	3	4	3.75		3	3	3	3	3.00	
						*3.38**	medium					*3.88**	medium					*3.00**	medium
8	8	4	4	4	4	4.00	high	5	4.5	4	4	4.38	high	4	4	4	4	4.00	high
9	9	3	3	3	3	3.00	low	3	4	3	4	3.50	medium	2	2	3	3	2.50	low
10	10	3	3	3.5	3	3.13	low	3	3	3.5	3	3.13	low	3	2	3	3	2.75	low
11	11	4	3	3	4	3.50	medium	3	3	3	4	3.25	low	4	2	2	3	2.75	low
12	12	4	3	3.5	3	3.38	medium	4	3	4	3	3.50	medium	4	3	3	3	3.25	medium
13	13a	3	3	3.5	3	3.13		3	2	3	3	2.75		3	3	2.5	3	2.88	
	13b	3	4	3.5	3	3.38		4	4.5	4	4	4.13		3	3	3	3	3.00	
	13c	2	2	3	3	2.50		2	1.5	3	3	2.38		2	2.5	3	3	2.63	
	13d	2	3	3	3	2.75		2	2	3	3	2.50		3	3	3	4	3.25	
						*3.29**	low					*3.65**	medium					*3.09**	medium
14	14	2	2	3	3	2.50	low	2	2	2	2	2.00	low	3	2	3	3	2.75	low
15	15a	4	5	4.5	4	4.38		4	5	4.5	4	4.38		4.5	5	4.5	4	4.50	
	15b	4	4	4	4	4.00		4	5	4	4	4.25		2.5	2.5	2.5	2.5	2.50	
						*4.13**	high					*4.30**	high					*3.21**	medium
ICC [#]		0.61						0.62						0.53					
ICC_k [##]		0.86						0.86						0.82					

* in study areas containing more than one site composite scores were calculated for the enire exposure zone within these study areas: see section 3.7.2.2

[#] : intra-class correlation coefficient or inter-rater agreement, see section 3.7.2.1

[##] : reliability of the average score of four experts, see section 3.7.2.1

Notes: - underlined scores are those that have been changed during the expert panel meeting

- changes in scores and averaging of scores led for three sites (2, 11, 13a) to an overall score not lying within the range of the water and air scores.

- due to averaging of scores and categorising into tertiles it is also possible for a site to have an overall hazard category which is higher or lower than both water and air hazard category for the same site (site 1, 2, 11, 13).

Table 4.18: Final expert panel hazard scores – difference between highest and lowest expert score assigned to a site.

difference in score:	*OVERALL*	*WATER*	*AIR*
	number of sites:		
0	3	2	5
0.5	3	3	2
1	13	11	8
1.5	2	3	2
2	0	1	4
2.5	0	1	0
total	21	21	21

4.4 RISK OF CONGENITAL ANOMALIES IN RELATION TO HAZARD SCORING OF LANDFILL SITES.

4.4.1 Trend in odds ratios with hazard potential

This section describes the relationship between risk of congenital anomaly within 3 km from a site and the relative hazard potential of a site, as scored using the expert panel hazard scores (section 4.3). This relationship was investigated by analysing the trend in odds ratios for living within 3 km of a sites with both hazard category and hazard score assigned to a site.

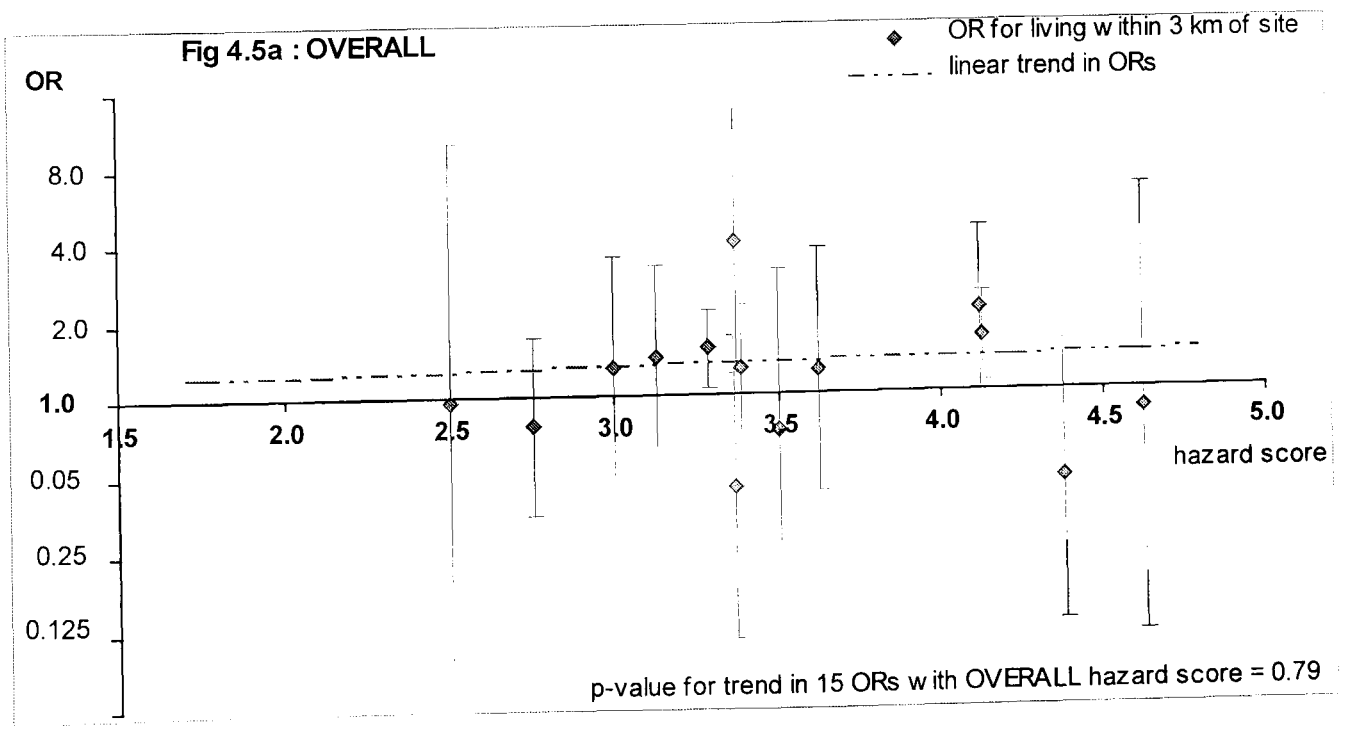
Table 4.19 shows for all non-chromosomal anomalies combined the odds ratios for living within 3 km from a landfill site compared to living further away from a site by low, medium, and high hazard categories each containing 5 study areas. There was no evidence for a trend of increasing odds ratio with increasing overall hazard (p=0.94) or air hazard (p=0.48). Odds ratios increase with increasing water hazard category (p for trend=0.05): from 0.86 (95% CI: 0.57-1.29) in the low hazard category, 1.43 (1.10-1.86) in the medium hazard category, to 1.60 (1.16-2.21) in the high water hazard category.

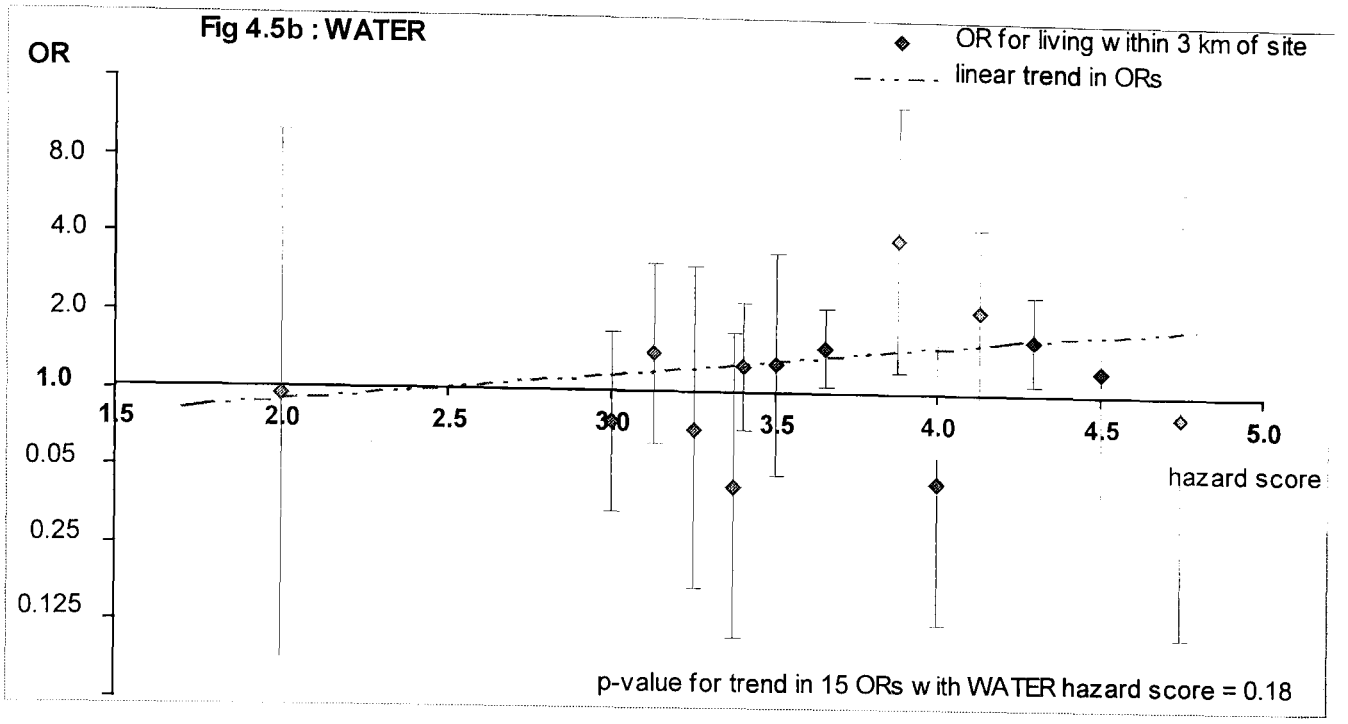
Similar results are found for the trend in the odds ratios of the 15 study areas with continuous hazard score: overall and air hazard again showed no trend whereas water hazard weakly suggests an increasing trend (p=0.18, Table 4.19 and Figure 4.5). Figures 5a, 5b, and 5c graphically show the odds ratios by continuous hazard score for overall, water and air respectively.

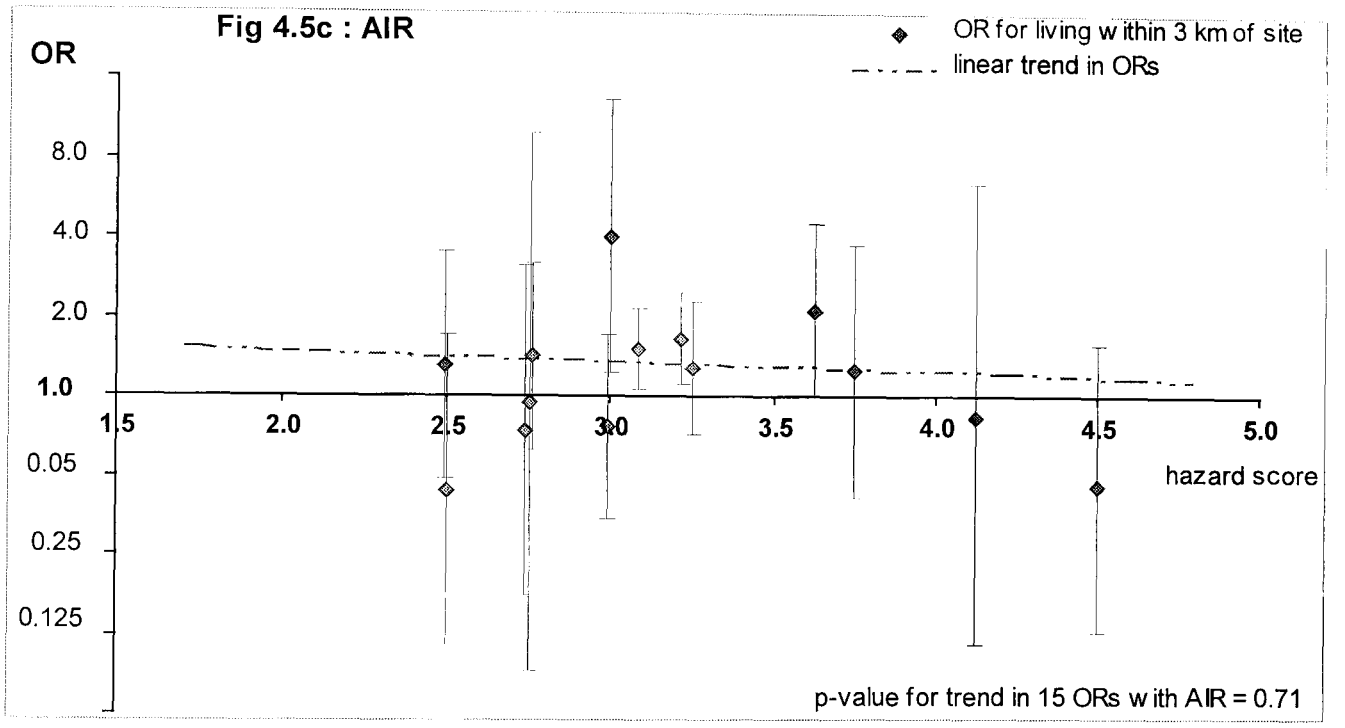
Table 4.19: Odds ratios for living within 3 km from a waste site by low, medium, and high hazard category – all non-chromosomal anomalies combined

hazard category	*study area*	*distance zone*	*cases*	*controls*	*OR**	*95% CI*
ALL STUDY AREAS		<=3km	295	511	1.33	1.11 - 1.59
undivided by hazard category (Table 4.6)		3-7 km	794	1855		
OVERALL hazard						
low	3, 9, 10, 13, 14	<=3km	128	206	1.40	1.07 - 1.84
		3-7 km	422	921		
medium	1, 2, 7, 11, 12	<=3km	80	147	1.15	0.78 - 1.69
		3-7km	167	400		
high	4, 5, 6, 8, 15	<=3km	87	158	1.48	1.07 - 2.04
		3-7km	205	534		
	trend in 3 ORs with hazard category				p=0.94	
	trend in 15 ORs with continuous hazard score				p=0.79	
WATER hazard						
low	1, 3, 10, 11, 14	<=3km	78	139	0.86	0.57 - 1.29
		3-7 km	180	278		
medium	5, 7, 9, 12, 13	<=3km	123	203	1.43	1.10 - 1.86
		3-7km	423	1064		
high	2, 4, 6, 8, 15	<=3km	94	169	1.60	1.16 - 2.21
		3-7km	191	513		
	trend in 3 ORs with hazard category				p=0.05	
	trend in 15 ORs with continuous hazard score				p=0.18	
AIR hazard						
low	1, 9, 10, 11, 14	<=3km	74	95	0.96	0.63 - 1.48
		3-7 km	194	265		
medium	3, 7, 12, 13, 15	<=3km	182	337	1.48	1.19 - 1.85
		3-7km	487	1317		
high	2, 4, 5, 6, 8	<=3km	39	79	1.23	0.75 - 2.02
		3-7km	113	273		
	trend in 3 ORs with hazard category				p=0.48	
	trend in 15 ORs with continuous hazard score				p=0.71	(negative trend)

Figure 4.5: Odds Ratios for living 0-3 km from a waste site in 15 study areas, by hazard score of the waste site – non chromosomal anomalies







Odds ratios for chromosomal anomalies showed a similar pattern over the various hazard categories to those for non-chromosomal anomalies (Table 4.20). Again only water hazard showed some suggestion of a trend in odds ratios with hazard category (p=0.19). Results were not statistically significant.

Neural tube defects, cardiac septal defects, and malformations of the great arteries and veins showed significantly raised odds ratios for living within 3 km of a site in previous analyses pooling data for all sites (section 4.2.2). Figure 4.6 shows for these three malformation subgroups the odds ratios for living within 3 km of a site by hazard category, and p-values for tests for trend in odds ratios both with hazard categories and with

continuous hazard score. No statistically significant trends in odds ratios with hazard category or hazard score were found. Numbers of cases in different hazard categories were generally small and confidence intervals wide, giving very limited power to test for differences between odds ratios. For neural tube defects odds ratios increased with air hazard category from 0.71 (95%CI 0.18-2.81) for low hazard, 1.93 (95%CI 1.23-3.02) for medium hazard, to 3.81 (95% CI 1.01-14.43) for high hazard, but this trend did not reach statistical significance (p for trend in 3 ORs = 0.11). Odds ratios for malformations of cardiac septa increased with water hazard (low hazard OR: 0.96, 95%CI 0.49-1.90; medium hazard OR: 1.57, 95%CI 1.02-2.42; high hazard OR: 2.02, 95%CI 1.07-3.83) and again this trend did not reach statistical significance (p for trend in 3 ORs = 0.13).

Table 4.20: Odds ratios for living within 3 km from a waste site by low, medium, and high hazard category – chromosomal anomalies

hazard	**OVERALL hazard**			**WATER hazard**			**AIR hazard**		
category	*N*	*OR**	*95% CI*	*N*	*OR**	*95% CI*	*N*	*OR**	*95% CI*
low	105	1.48	0.85 - 2.57	46	0.96	0.37 - 2.53	41	1.05	0.40 - 2.74
medium	51	1.28	0.56 - 3.29	108	1.55	0.91 - 2.63	139	1.51	0.97 - 2.34
high	48	1.65	0.83 - 3.29	50	1.66	0.85 - 3.23	24	1.15	0.36 - 3.61
trend in 3 ORs with hazard category:			p=0.83			p=0.19			p=0.78
trend in 15 ORs with hazard score:			p=0.55			p=0.28			p=0.96

* adjusted for soci-economic status and maternal age

Figure 4.6: Odds ratios for living within 3 km from a waste site, by low, medium, and high hazard category – malformation subgroups.

Figure 4.6a : Neural Tube Defects (N=130)

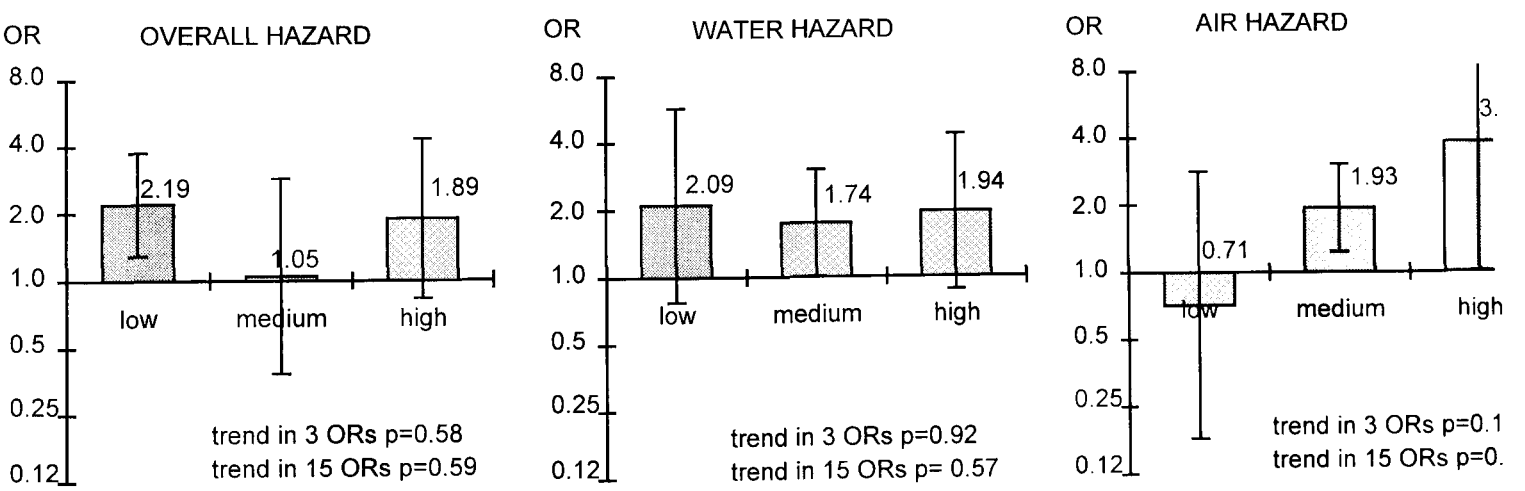


Figure 4.6b : Malformations of Cardiac Septa

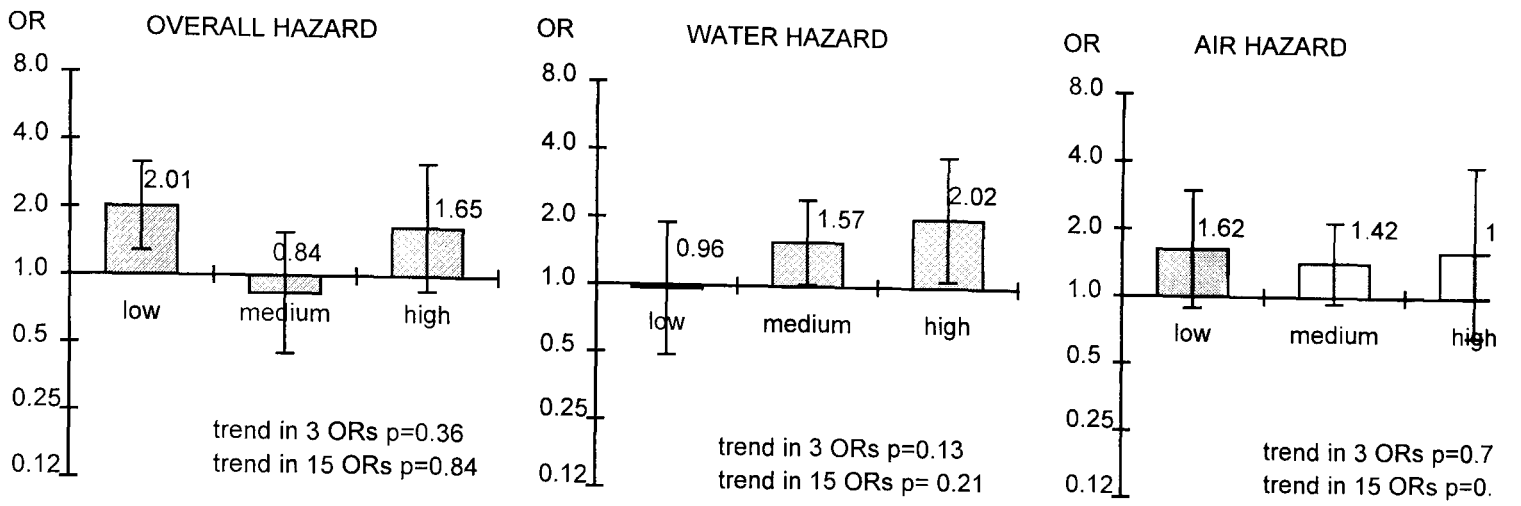
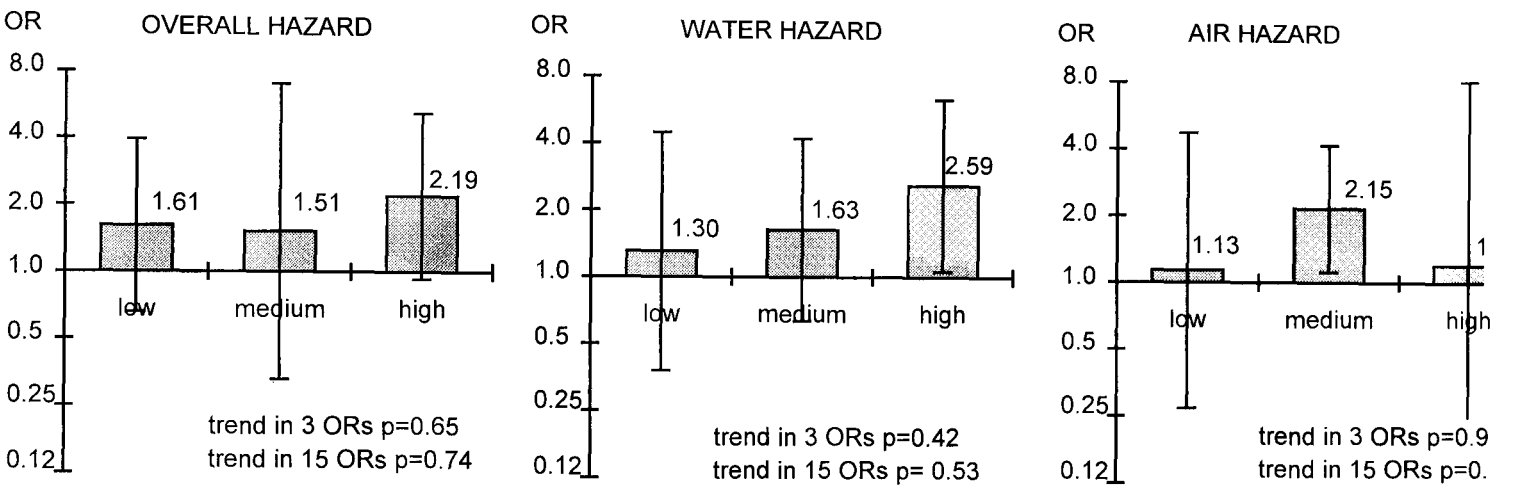


Figure 4.6c: Malformations of great arteries and veins



4.4.2 Hazard score in continuous distance models

Table 4.21 shows results of exploratory models incorporating hazard scores of sites (overall, water, and air) into the models of exponentially declining risk of non-chromosomal anomaly with distance. As explained in section 3.7.2.3 the risk next to the site (α) is proportioned according to the hazard score (H) of the sites. The rate of decline with distance (γ) is fixed at the value (0.28) estimated from the model including distance only (section 4.2.3). Table 4.21 shows that none of the hazard scores improved the fit of the model substantially: the deviance of the model without hazard score is very similar to that of models incorporating overall, water, and air scores. Incorporating water hazard scores slightly improved the fit of the model (smaller deviance), overall hazard scores did not change the model fit, and air hazard scores very slightly worsened the model fit. Interpretation of the differences between

models is extremely difficult since no statistical tests are available to test for differences between models with equal numbers of parameters (section 3.7.2).

Table 4.21: Exponential excess risk model incorporating both distance and hazard score of sites - non-chromosomal anomalies

*Model**			*α*	*Deviance*	*df*	*p-value*	*Dev model 1 - dev model 2 (likelihood ratio)*
1	without hazard score**	{1+ α exp(-0.28d) }	1.18	4201.69	1	0.0009	
2a	overall hazard score (H_o)	{1+ (αH_o) exp(-0.28d) }	1.66	4201.69	1	0.0009	0.00
2b	water hazard score (H_w)	{1+ (αH_w) exp(-0.28d) }	1.67	4200.72	1	0.0005	0.97
2c	air hazard score (H_a)	{1+ (αH_a) exp(-0.28d) }	1.82	4201.75	1	0.0009	-0.06

d=distance from site, H_o=overall hazard score, H_w=water hazard score, H_a=air hazard score

* adjusted for maternal age and socio-economic status

** model equivalent to model 3 in Table 4.9

4.5 SOCIO-ECONOMIC VARIATION IN RISK OF CONGENITAL ANOMALIES

This section investigates the relationship between socio-economic status and risk of congenital anomalies in detail using data from four U.K. centres (Glasgow, Northern Region, North Thames (West), England & Wales Down Syndrome Register). These analyses are based on a total of 667 non-chromosomal cases, 191 chromosomal cases and 1764 controls. Socio-economic status was measured using quintiles of the Carstairs deprivation index of small areas in which the cases and controls were born, as explained in section 3.5. Two cases and three controls lived in areas where deprivation could not be classified. 10% of all U.K. controls were born in deprivation quintile 1, 39% in quintile 5.

Table 4.22 shows the odds ratios for the most deprived deprivation quintile compared to the most affluent deprivation quintile for non-chromosomal anomalies, chromosomal anomalies and selected malformation subgroups.

A greater risk of non-chromosomal anomalies is found with increasing socio-economic deprivation (Table 4.22). The risk in the most deprived quintile of the deprivation index was 40% higher than in the most affluent quintile after adjustment for potential confounding factors (adj. OR 1.41; 95%CI 1.04-1.91). Adjustment for confounders did not substantially change the unadjusted odds-ratio estimate (unadj. OR 1.33; 95%CI 1.01-1.75). Figure 4.7 shows graphically the odds ratio estimates for non-chromosomal anomalies in each deprivation quintile compared to the most affluent quintile (quintile 1).

Table 4.22: Odds ratios for most deprived versus most affluent deprivation quintile - U.K. centres

Malformation group	*N*	*OR**	*95% CI*
All Non Chromosomal Anomalies	665	1.41	1.04 - 1.91
Neural Tube Defects	107	1.23	0.63 - 2.37
Other Central Nervous System Defects	33	1.34	0.41 - 4.40
All Cardiac Malformations	230	1.59	0.98 - 2.59
malformations of cardiac chambers and connections	30	1.94	0.53 - 7.13
malformations of cardiac septa	135	2.82	1.43 - 5.56
malformations of cardiac valves	74	1.49	0.66 - 3.36
malformations of great arteries and veins	77	1.04	0.48 - 2.23
Oral Clefts	73	0.95	0.44 - 2.05
cleft palate	29	0.95	0.29 - 3.09
cleft lip/palate	44	0.97	0.36 - 2.63
Tracheo-oesophageal Anomalies	20	1.53	0.29 - 7.95
Digestive System Anomalies	44	3.53	1.11 - 11.18
Renal and Urinary Anomalies	78	1.51	0.68 - 3.35
Limb Reduction Defects	27	1.22	0.34 - 4.32
Abdominal Wall Defects	20	1.57	0.35 - 7.05
Multiple Malformations	56	2.58	0.95 - 7.01
All Chromosomal Anomalies	191	0.73	0.44 - 1.21
Down Syndrome	139	0.80	0.44 - 1.45

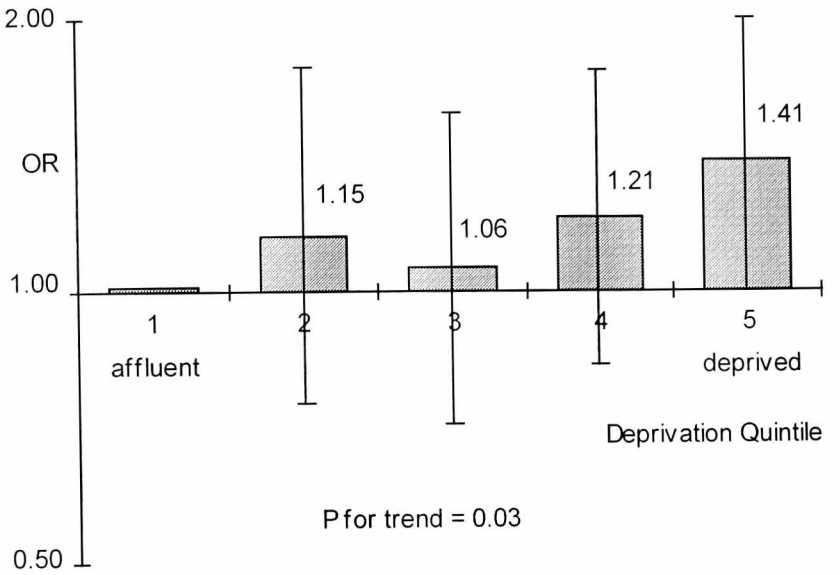
* estimated from log-linear model and adjusted for maternal age, year of birth, study region, and distance from landfill site.

Most non-chromosomal malformation subgroups, with the exception of oral clefts, also showed raised odds ratios in the most deprived compared to the most affluent areas (Table 4.22). However, confidence intervals were wide and included unity in most subgroups. Statistically significant trends of increasing risk with increasing deprivation were found only for malformations of the cardiac septa (p=0.003; OR quintile 5 versus quintile 1 2.82, 95% CI 1.43-5.56) and malformations of the digestive system (p=0.03; OR 3.53, 95% CI 1.11-11.18). All cardiac defects (p=0.06; OR 1.59, 95% CI 0.98-2.59) and multiple malformations (p=0.06; OR 2.58, 95% CI 0.95-7.01) showed trends of borderline significance.

Statistically significant trends of decreasing risk with increasing deprivation were found in unadjusted analyses for Down Syndrome (p=0.002; OR quintile 5 versus 1: 0.47, 95% CI 0.29-0.76) and all chromosomal malformations combined (p=0.0003; OR 0.46, 95% CI 0.30-0.70) (not shown in Table 4.22). Maternal age is a strong potential confounding factor in this relationship. The percentage of older mothers (30 years or over) was higher in more affluent areas: 46% (including 10% over 35 years) in the most affluent quintile compared to 19% (including 5% over 35 years) in the most deprived quintile (p<0.0001). After adjustment for maternal age the odds ratio for the most deprived versus the most affluent quintile was 0.80

(95% CI 0.44-1.45) for Down Syndrome and 0.73 (95% CI 0.44-1.21) for all chromosomal malformations combined (Table 4.22). More finely stratified adjustment for maternal age (<30, 30-34, 35-37, 38-40, >40) did not bring the odds ratios closer to unity.

Figure 4.7: Odds ratios for non-chromosomal anomaly (N=665) by deprivation quintile – U.K. centres



CHAPTER 5

DISCUSSION AND CONCLUSIONS

This chapter discusses the methodology and findings presented in previous chapters and follows the structure of the results sections (chapter 4): risk of congenital anomaly in relation to distance of residence from landfill sites, risk of congenital anomaly in relation to hazard potential scoring, and socio-economic variation in risk of congenital anomaly. General conclusions are summarised in section 5.4.

5.1 RISK OF CONGENITAL ANOMALY IN RELATION TO DISTANCE OF RESIDENCE FROM HAZARDOUS WASTE LANDFILL SITES

Results, presented in section 4.2, show a statistically significant 33% (95% CI 11%-59%) increase in risk of non-chromosomal congenital anomalies for mothers living close (within 3 km) to hazardous waste landfill sites compared to those living further away (3-7 km). Data also suggest that the risk of non-chromosomal anomalies declined fairly consistently with increasing distance from the waste site. Risk of chromosomal anomalies was raised close to the waste sites compared to further away but did not reach statistical significance and showed little evidence of a decline with continuously increasing distance. Malformation groups that showed statistically significant increased risks for residence close to hazardous waste landfill sites were neural tube defects, malformations of the cardiac septa, and anomalies of the great arteries and veins. The following sections (5.1.1-5.1.3) assess the influence bias and confounding factors may have had on these findings. Section 5.1.4 discusses the interpretation of the findings and evaluates the likelihood that the associations found are causal.

5.1.1 Bias in exposure measurement

Distance of residence from sites is commonly used as a surrogate for exposure in epidemiological investigations of point sources of environmental pollution. Section 2.4 showed that many waste site studies have used distance based exposure measures. In the

present study, the use of distance of residence at birth to landfill sites as surrogate measure of exposure to contamination from landfill sites may have led to misclassification of exposure for the following reasons :

- In the present study 'exposed' and 'unexposed' areas were defined on the basis of a 3 km cut-off. Although defined on the advice of landfill experts, this cut-off may be inaccurate in representing the distance from the landfill sites up to which contamination may occur and residents may be exposed. As discussed in previous chapters (2.2, 3.3) little is known about how far contamination from landfills may extend. Also, this distance is unlikely to be the same for different sites and will depend on the pathway of exposure. Groundwater when contaminated may carry persistent pollutants over a long distance, air pollutants are likely to be diluted quickly in ambient air (section 2.2). Analyses of risk of congenital anomaly in relation to continuous distance from landfill sites avoided the problem of an arbitrary cut-off.

- The use of distance of residence does not take account of possible directional effects in contamination from landfill sites and thereby possible exposure of residents. Groundwater contamination is not likely to spread evenly over all directions but will follow the direction of the groundwater flow. Air pollution will be carried in the direction of the wind, although it is not always certain that areas in the direction of the predominant wind are those that encounter the highest exposures. Windstill days may be the days at which pollutants are less diluted and may be more important in determining high exposure areas. In the study of congenital anomalies, days with maximum exposure (possibly windstill days) may be of more importance than days with average exposure (due to the prevailing wind), because teratogenic impacts are thought to results from exposures above threshold levels at a specific time in embryonic development (section 2.3.1). There is some evidence from air pollution dispersion modelling that ground level sources (sources emitting pollutants at ground level, such as the surface of a landfill) fit a model of circular dispersion around a site relatively well, better than sources emitting pollutants through a stack, such as incinerators (Gev Eduljee, Roger Barrowcliffe: personal communication). A directional plume of contamination from a site would usually still result in higher exposures nearer to sites than further away but would result in a large proportion of residents in the nearby zones being wrongly classified as 'exposed'.

Current knowledge about spatial exposure patterns from landfill sites is limited which makes it difficult, in the absence of direct exposure measurements, to improve on the assumption of a circular 'exposure' pattern. Dispersion modelling could be useful in validating this assumption and if necessary, improving the spatial model of distribution of possible exposure around a landfill.

- As discussed in chapter 2.3 only exposure during the first few months of pregnancy, or even the period before conception may lead to the development of major congenital malformations. In the case of exposure to chemical compounds which bioaccumulate in the body, the length of residence of the mother before pregnancy may also be important. In this study distance of residence *at birth* was used to measure exposure. If women moved between early pregnancy and birth this would have led to misclassification of exposure. Information on mother's address during early pregnancy, or length of residence in the study areas was not available. There are few estimates in the literature of the proportion of women who move during pregnancy. Studies in the U.S. have estimated that 20-25% of pregnant women move during pregnancy (Schulman et al, 1993; Shaw and Malcoe, 1992). Similar proportion of women has been estimated to move during pregnancy in the U.K.(Dolk, 1997). Mobility patterns elsewhere in Europe may be different. There is no reason to believe that mothers of cases in this study would have been more likely than control mothers to move during their pregnancy. Concern about landfill sites may have led to more migration in the study areas, but it is unlikely that people with high risk of having babies with congenital anomalies moved out more frequently than others because of these concerns. Around a quarter of sites had been subject of some type of public concern, but at none of the sites concerns were specifically related to birth defects.

- The use of distance of residence to define exposure does not account for the fact that people may spend a substantial amount of their time each day away from the residential location. There was no information available in this study on the amount of time spent at home or away from home by the mothers of cases and controls. Again there is no reason to believe that patterns of daily activity were different for case and control mothers.

- In order to select cases and controls born within the 7 km study areas defined for this study, the place of residence of the mother had to be located on maps, either through automatic linkage of postcodes and addresses to map references or manually. Inaccuracies in locating cases and controls may have led to misclassification of distances within the study areas, but only if cases and not controls were systematically located closer to the landfill than their true location (or controls further away) could this have explained the finding of excess risk near landfill sites. I am confident that no systematic error of this kind occurred in the data. In all centres the same methods were employed to locate both cases and controls within study areas. Errors in locating cases or controls around the edge of study areas, or errors in defining the edge of the study area, could have resulted in an excess or deficit of cases or controls in the outer distance band. Comparison of the 0-3 km band with a 3-6.5 rather than 3-7 km band gave an unadjusted odds ratio for non-chromosomal anomalies of

1.33 (95% CI 1.11-1.59), similar to the original 0-3 versus 3-7 km comparison, suggesting that possible errors in the location of cases and controls around the edge of the study areas did not explain the excess risk found near landfill sites.

The use of distance of residence at birth from landfill sites as surrogate for landfill exposure may have led to misclassification of exposure through any of the above reasons. There is no reason however to conclude that misclassification was non-random, i.e. that it affected cases differently than controls. Random misclassification of exposure will usually decrease the power of a study to find a true effect and bias the true relative risk towards null(Armstrong, 1998).

5.1.2 Confounding

5.1.2.1 Socio-economic status

Socio-economic status is potentially an important confounder of the relationship between residence near landfill sites and risk of congenital anomaly. Results for U.K. centres presented in section 4.5 and discussed in section 5.3, show that more deprived populations may have a higher risk of congenital anomalies of non-chromosomal origin and some specific malformation subgroups. There was no evidence however for more deprived people to consistently live closer to waste sites in the EUROHAZCON study areas. Indeed, data suggest that in the study area with the largest population and a significant increased risk within the 3 km zone, study area 13, populations living further away from sites were more deprived than those living close by. Adjustment for socio-economic status in statistical analyses did not substantially shift the odds ratio estimates in this study either for chromosomal or non-chromosomal anomalies, indicating a limited effect of socio-economic status as a confounding factor. Risk estimates in individual malformation subgroups were also not influenced substantially by socio-economic status adjustment, even in the malformation subgroups which showed significant trends of greater risk with increasing socio-economic deprivation (section 4.5: cardiac septa, digestive system anomalies).

From the above, it seems unlikely socio-economic status substantially confounded findings. However, inadequate measurement of socio-economic status in this study may have led to inadequate control for socio-economic confounding and the presence of residual confounding. The lack of standardised socio-economic classifications in Europe hampered

the ability to employ the same method of control for socio-economic confounding in each country, but statistical models allowed for any socio-economic status effect to vary between countries. Although adjustment for socio-economic status generally resulted in a shift in odds ratios towards unity, the shift was small, especially in pooled analyses, and it seems unlikely that residual socio-economic status would explain the whole of the increase in non-chromosomal congenital anomaly risk.

5.1.2.2 Maternal age

Maternal age is an important risk factor for chromosomal anomalies, but not clearly for non-chromosomal anomalies as discussed in section 2.5.3. Data from this study on risk of congenital anomaly by maternal age (section 4.2.1) also show this. There is little evidence that older mothers lived closer to landfill sites in the EUROHAZCON study areas which makes it unlikely that any increase in risk of congenital anomalies, chromosomal or non-chromosomal, near waste sites was due to maternal age. Adjustment for maternal age had little impact on the risk estimates for non-chromosomal anomalies. Adjustment of odds ratios for chromosomal anomalies resulted in an increase in the estimates, away from unity. This suggests that if any residual confounding by maternal age was present in these results, for example due to grouping of maternal ages in five age bands, the true relative risk for chromosomal anomalies would be greater than the relative risk reported in this thesis.

5.1.2.3 Other sources of environmental pollution

It is possible that confounding occurred by other sources of exposure to environmental pollutants located near landfill sites in the study areas. It is conceivable for example that hazardous waste landfill sites are located in areas of a generally more industrial nature. Also, hazardous waste landfill sites may be located near other landfill sites, for example municipal landfill sites which, as discussed in chapter 2.1, may pose similar hazards to so-called 'hazardous' waste sites. In most of the study areas there was no information available about whether industrial sites, municipal landfills, or other possible sources of environmental pollution were located nearby the study sites. For sites in England some information was obtained about nearby industrial sources of pollution from the Chemical Release Inventory (CRI) (CRI, 1996; Friends of the Earth, 1999). The CRI documents releases from major industrial sources into the environment. The CRI started in 1991 but is only since 1996 complete in covering all main sectors of industry. Large industries are required to submit annual records of water, air and soil releases of chemical compounds to the CRI. Table 5.1

shows the number of CRI sites that were located in1996 within the English EUROHAZCON study areas. Since study periods in the current study finished at the end of 1993 it is not certain that the industries were present during the study periods. In all study areas more CRI sites were located within 3-7 km than within 0-3 km from the landfill sites. Study area 13 contained the largest number of CRI sites within 3 km, one of which, a chemical works, was located very close (0.4 km) to one of the landfill sites. Study area 13 also contributed the largest number of cases and controls to this study. Information in the CRI suggests releases of benzene, VOCs and particulates to air, and releases of cadmium, lead and mercury to water associated with this chemical plant.

Table 5.1: Industrial sites within English EUROHAZCON study areas, as documented in the 1996 Chemical Releases Inventory

Study area	*Number of industries* 0-3 km	3-7 km	*Details of industries within 3 km* type of industry	distance from nearest landfill site	*chemcial releases documented*
3	0	2			
4	0	0			
12	0	1			
13	3	4	chemical works	0.4 km from site 13c, 2.8 km from 13b	air: benzene, VOCs, particulates water: cadium, lead, mercury, zinc
			cement manufacture	1.9 km from site 13c	air: asbestos, particulates
			chemical works	2.4 km from site 13c	air: hydrgen sulphide, particulates, VOCs
14	0	1			
18	2	3	gas works	2.9 km from site 18	air: ethanethiol
			oil/power plant	3 km from site 18	air: CO, NO2, SO2, particulates; water: cadmium, mercury
19	0	2			
20	2	6	?	1.4 km from site 20	none in 1996
			?	2.7 km from site 20	none in 1996

There have been few studies of congenital anomaly risk near any kind of industrial site which makes it difficult to assess the potential confounding effect of the presence of industrial sites near the study sites. Studies of malformation risk near vinyl chloride plants (Centre for Disease Control, 1975; Edmonds et al, 1978; Edmonds et al, 1975; Rosenmann et al, 1989; Theriault et al, 1983), incinerators (Jansson and Voog, 1989; Scottish Home and Health Department, 1988), and metal smelters (Nordstrom et al, 1979; Wulff et al, 1996) have not been conclusive. A study in New York State found an increased risk of congenital anomaly related to residence near metal and solvent emitting industries rather than to residence near hazardous waste sites (Marshall et al, 1997). The possibility remains that some of the excess risk of congenital anomaly found in study area 13 may have been due to the industrial pollution sources located in this area. Further study of risk of congenital anomaly in

relation to other pollution sources is recommended to place the current findings regarding landfill sites into context.

Table 5.1 shows that in 3 of the eight English study areas industrial sites were located near the landfill sites under study. It is unlikely that industrial sites were located near landfill sites across all other study areas and it seems therefore unlikely that the pooled results can be explained entirely by such sources of exposures.

5.1.2.4 Parental occupation

Occupation of the mother may be a confounding factor in this study, since mothers living near landfill sites may work at the landfill sites or in industries located near sites, where they may be exposed to teratogenic chemicals. However, as shown in section 2.3, few occupational exposures have as yet unequivocally been linked to risk of congenital anomaly. It seems unlikely that across all study areas a large enough proportion of women living near landfill sites would be exposed to occupational teratogens in doses high enough to explain the increase in risk of congenital anomalies found in pooled analyses.

A further possibility is that occupational exposure of fathers at the landfill or nearby industries resulted in an increase of congenital anomalies for residents near the sites. This has for example been postulated as a mechanism for the increase in childhood leukaemia incidence near nuclear installations (Gardner et al, 1990). Although there is increasing interest in the possibility that paternal exposures to teratogenic and mutagenic compounds may cause congenital anomalies in the offspring, there is as yet little evidence for this in humans (Olshan and Faustman, 1993; Sever, 1995). Mechanisms proposed for 'male-mediated teratogenicity' include *1)* direct effects on paternal germ cells, and *2)* secondary maternal exposure through seminal fluids or exposures brought home by the father(Olshan and Faustman, 1993). Again it seems unlikely that enough fathers living near landfill sites were occupationally exposed to explain the increase in risk of congenital anomalies in this study.

5.1.2.5 Other risk factors

Risk factors for congenital anomalies which were not measured in this study could have acted as confounding factors. Very few external factors have clearly been established as risk factors for congenital anomalies as discussed in section 2.5, and only a small percentage of

congenital anomalies can currently be attributed to established risk factors. Factors which have as yet not unequivocally been linked to congenital anomalies, such as smoking and moderate alcohol consumption, as well as other, unknown risk factors could of course play a confounding role. However, for most risk factors, established or not, there is little reason to assume that they would occur more frequently in the populations near landfill sites than further away, other than through differences in socio-economic status. Potential for socio-economic confounding has been discussed in previous sections (5.1.2.1). Ethnicity may be one factor that could, independently of social class, be geographically related to landfill sites. As discussed in chapter 2.5 South Asians generally have a higher risk of having babies with birth defects, independently of socio-economic status. In the U.K. around 4% of all births in 1995 were to mothers born in India, Pakistan, and Bangladesh (Office for National Statistics, 1997). South Asian populations in other European countries are likely to be smaller. Information about the ethnic origin of residents near the waste sites in EUROHAZCON study areas was not available, but it is unlikely that this percentage is high enough in any of the study areas to explain the increase in risk of birth defects near landfill sites.

5.1.3 Other sources of potential bias

5.1.3.1 Bias in ascertainment and selection of cases

Geographical variation in case ascertainment may have led to bias in this study, for example if there was more complete reporting of congenital anomalies closer to sites. One possibility is that public concerns about landfill sites led to higher reporting of congenital anomalies near sites. The study used routinely collected malformation data however, which were collected with no knowledge of the study hypothesis and from multiple information sources. Moreover, as discussed in section 5.1.1, concerns reported in relation to study sites were not specifically related to birth defects. Also, congenital anomalies included in this study were major malformations for which a high completeness of ascertainment can generally be assumed in routine registrations. Cases of isolated minor anomaly, which may be more subject to ascertainment bias, were not included in the study.

If hospital catchment areas were spatially related to landfill sites, and reporting of congenital anomalies did vary between hospitals, this may have led to bias. Appendix 10 shows hospital of birth of cases and controls in 0-3 and 3-7 km bands in 9 study areas where information about hospital of birth was available for both cases and controls. Appendix 10

shows that in most of these study areas cases tended to be born in different hospitals than controls. This may indicate that case pregnancies are referred to different (i.e. more specialist) hospitals than controls, and/or that ascertainment of congenital anomaly cases varied between hospitals. Analysis of the spread of hospital of birth of cases between the 0-3 km and 3-7 km distance bands, did not indicate a large difference between the two distance bands in the percentage of cases reported in each of the hospitals. Information on hospital of birth as shown in Appendix 10 is difficult to interpret because of small numbers of cases and controls born in each hospital and distance band. From these data however there is no evidence that ascertainment differences between hospitals explain the increase in risk of congenital anomaly near landfill sites.

5.1.3.2 Bias in control selection

The unbiased selection of controls is essential to any case-control study design. In this study spatially unbiased selection of controls was essential: selection of controls had to be independent of their distance of residence from the landfill sites. The protocol for control selection paid special attention to selection of an unbiased set of controls, and methods were tested in the pilot study, as discussed in methods section 3.3.4. In one of the study centres (Glasgow) a bias was detected in the pilot study due to records in the birth database being spatially ordered. In the pilot study, selection of the first records on the day after the case was born resulted in an excess of controls in one part of the study area. Methods for the selection of controls in Glasgow were changed for the main study. In other centres there was no evidence for this type of bias.

As a further check of control selection methods, numbers of controls selected for the study were compared to total numbers of births in study areas 12, 13, 14, and 15 where the total number of births in each distance zone was known. There was no statistically significant difference in any of these study areas between the 0-3 and 3-7 km bands in the percentage of births and percentage of controls selected. However, in areas 13 and 15, two areas which showed raised odds ratios for non-chromosomal anomalies, a non-statistically significant deficit of controls was found in the 0-3 km zone. In area 13, 15.3% of controls and 17.6% of births were located in the 0-3 km band (χ^2 2.67, p=0.12). In area 15, 25.5 % of controls compared to 29.4 % of all births were located in the 0-3 km band (χ^2 2.94, p=0.09). If expected numbers of controls on the basis of the total number of births are used in the analysis of malformation risk, unadjusted odds ratios for non-chromosomal anomalies in these study areas are no longer statistically significant (study area 13: OR 1.29, 95CI% 0.91-

1.83; study area 15: OR 1.30, 95%CI 0.87-1.94). The pooled odds ratio for non-chromosomal anomalies still shows a statistically significant excess in cases (unadj OR 1.25, 95%CI 1.06-1.47). Since in both these areas control selection was entirely random and no systematic errors were suspected, the deficits reported can be regarded as being due to chance. In the two other study areas tested (12 and 14) no deficit was found. Random selection in the other study areas may also have given chance deficits or excesses of controls in certain distance bands, but it was not possible to check for such variations.

5.1.4 Interpretation of findings

5.1.4.1 Evidence for exposure of residents to landfill site contamination

A main problem in interpretation of the findings of this study is the lack of evidence that residents near landfill sites in general or near sites included in the study, are actually exposed to pollution from these sites.

Review of existing literature showed that although the presence of toxic chemical compounds has been demonstrated in leachate and landfill gas released from landfill sites, information about exposure of residents near landfills to these compounds is almost completely lacking (section 2.2). Section 2.2 showed that high contamination levels, mainly of organic solvents, have been detected in drinking water wells near certain landfill sites in the U.S. Concentrations of volatile organic compounds (VOCs, many of which are also organic solvents) may be high in pure landfill gas, but these are thought to be diluted considerably within a short time of being released from the landfill surface. The few studies which have measured levels of VOCs in communities near waste sites have found little evidence of high concentrations of individual chemicals. Information on individual chemical concentrations does not take account however of possible effects of exposure to mixtures of similar volatile organic compounds. Information on concentrations of other possible contaminants (for example heavy metals, PCBs), is extremely limited. Direct exposures studies are scarce and have generally tended not to find strong evidence for exposure of residents near waste sites, although there is some evidence from biomarker studies suggesting that exposure of landfill workers and residents to genotoxic and hepatotoxic chemicals has occurred near certain sites (see further section 2.2). In chapter 2.4 some indications were found that residence near certain landfill sites may be associated with

health risks, suggesting again that exposure of human populations may occur near certain landfill sites.

In the present study, information on the occurrence of off-site contamination from landfill sites was not generally available in readily usable form. At few sites site investigation reports summarising monitoring data were available. Also, monitoring data varied hugely between sites with regard to frequency of monitoring, the types of chemical compounds monitoring, and the location of the monitoring points. Some sites however had been associated with off-site contamination, as described in section 4.3.1: at 7 sites groundwater pollution had at some stage been documented, at two sites air measurements showed the presence of volatile organic compounds, and at one site chromium contamination was found in soil and air. At 7 sites residents had complained about smells from the landfill site, indicating the release of landfill gas possibly containing trace VOCs. At other sites, information about off-site contamination was not available.

It is also not known what the most likely pathways of exposure are at each of the study sites. Ingestion of potential drinking water is in most of the study areas an unlikely pathway since water supply in the participating regions comes mainly from public supply and local groundwater is unlikely to be consumed by local residents. Private drinking water wells were however reported to be present within 7 km of eleven of the study sites, and within 3 km of six of these. It is not known whether these private wells provided water for domestic uses, how many people used the wells, or whether they were in the direction of the groundwater flow from the waste site. Alternative pathways would be landfill gas, dust and particle emissions from the sites resulting in contamination of ambient air, or possibly direct contact of residents with contaminated soil, surface water, or consumption of home grown foods.

Whether or not possible off-site environmental contamination reached residential populations living nearby the sites in this study, and if so, in what doses and via which pathways, is not known. Existing literature on contamination, human exposure, or human health effects from landfill sites is insufficient to aid conclusions of the likelihood that exposure of local residents occurred in this study. The hazard potential scoring, further discussed in section 5.2, was developed to assess the relative likelihood of exposure at the study sites, based on available information about site characteristics.

5.1.4.2 Non-chromosomal anomalies

The finding of an excess risk of non-chromosomal anomaly near hazardous waste landfill sites cannot be explained by obvious confounding factors, although lack of information on exposure from landfill sites and on possible other sources of exposure in the study areas seriously limit the interpretation of these findings, as discussed in previous sections. The use of surrogate exposure measurement is likely to have led to misclassification of exposure but this would usually result in a lower relative risk than the true relative risk. The possibility that the findings were due to chance can never be excluded in one epidemiological study. The finding of a fairly consistent decline in risk with continuous distance reduces the likelihood that the whole of the association found in pooled analyses comparing dichotomous distance bands was due to chance and strengthens evidence for causality.

The literature reviewed in section 2.4 showed that some previous multi-site and single site epidemiological studies of congenital malformation risk among residents near landfill sites have shown increased risks near sites (Croen et al, 1997; Geschwind et al, 1992; Goldman et al, 1985; Shaw et al, 1992). Numbers of studies are too few however, and results too inconsistent to greatly strengthen conclusions of causality in the present study. Literature on teratogenic effects of individual chemical compounds which may be present in landfill pollution (section 2.3), shows that although many such compounds have shown teratogenic potential in animal experiments, evidence from human studies is very scarce, and again this body of literature does not greatly aid the interpretation of the current findings. Few environmental chemicals have been established as human teratogens and those that have, organic mercury and PCBs, have not shown to cause gross structural malformations. There is some evidence to suggest that solvents, many of which are commonly present in landfill gas and leachate from landfill sites, may cause malformations in humans. This evidence originates mainly from solvent abuse case studies and occupational studies, where exposure are likely to be higher than potential landfill exposures.

In theory both maternal and paternal exposure to chemicals may result in congenital anomalies in the offspring, as discussed in sections 2.3 and 5.1.2.4. It is not possible in this study to distinguish between the two. In the absence of strong evidence regarding paternally mediated effects, potential maternal exposures seem of most concern in relation to congenital anomaly risk near landfill sites.

The possibility has been raised that exposure to infectious rather than chemical agents from landfill sites may be responsible for the raised risk of congenital anomalies. There has been

very little study of this possibility. One study of enteric viruses in landfill leachate did not detect viruses in leachate samples from a number of municipal waste sites in North America, and concluded that such viruses would be filtered out in soil and diluted in groundwater and would not constitute a public health hazard (Sobsey, 1978). Certain infectious agents have been found to cause congenital anomalies birth defects (see section 2.5). Enteric viruses, the most likely infectious agents present at municipal landfills, have not been amongst these.

If we assume that the association between living near hazardous waste sites and non-chromosomal congenital anomalies is causal, 25% of cases of non-chromosomal anomaly that occur within 3 km of hazardous waste landfill sites could be considered 'attributable' to waste site exposure : in the 15 study areas included in this study there were 295 cases of non-chromosomal congenital anomaly within 3 km of sites, 74 of these occurred in excess of what would have been expected if risk of congenital anomaly were the same close to and further away from the sites. Prevalence rates of non-chromosomal anomaly cases selected for this study ranged from 8.0 to 10.8 per 1,000 births in the Glasgow and Northern Region study areas where total numbers of births were known. Using the total prevalence rates across these areas (8.9 per 1,000 births) to estimate the general prevalence of malformations selected for this study, an extra 2 cases per 1,000 births within 3 km of landfill sites are estimated to occur in excess of the expected prevalence.

In the general population, the proportion of congenital anomaly cases that could be attributed to waste site exposures, assuming again causality of the findings, would be lower, since only a small proportion of the entire population may live within 3 km of a waste site. Calculation of the proportion attributable risk in the general population requires an estimate of the proportion of the population living close to such sites. In the U.S. it has been estimated that around 4 million people (around 1.5% of the population) live within 1 mile of a National Priority List hazardous waste site (National Research Council, 1991). Such estimates are not available for Europe and may of course be very different here. If 1% of the population lived within 3 km of hazardous waste landfill sites similar to those studied in this study, and the relationship found in this study was causal, 0.32% of all cases of non-chromosomal congenital anomaly occurring in the general population would be attributable to living near such waste sites. If 10% of the population lived within 3 km of hazardous waste sites or similar exposure sources, the attributable risk in the general population would be around 3%. This is in the same order of magnitude as the percentage of congenital malformations estimated to be caused by all maternal diseases and infections combined (Kalter and Warkany, 1983; see section 2.5). This means that a small, but not negligible, percentage of congenital anomaly cases might theoretically be avoided if all exposure to contamination

from hazardous waste landfill sites was prevented, again assuming a causal relationship. The fairly small population attributable risk does not of course take away from the potential importance of the findings in individual risk terms.

5.1.4.3 Chromosomal anomalies

There was in this study no clear increase in risk of chromosomal anomalies near hazardous waste landfill sites, nor in the risk of Down syndrome or non-Down syndrome chromosomal anomalies, the two main chromosomal anomaly subgroups analysed. Analyses combining all 20 study areas where data on chromosomal anomalies were available show a non-statistically significant increase in risk (OR 1.29, 95%CI 0.79-2.10) close to sites compared to further away for all chromosomal anomalies. In study areas 1-15 (the same study areas on which analyses of non-chromosomal anomalies were based) the relative risk for chromosomal anomalies near sites was higher (OR 1.41, 95%CI 0.97-2.04), and nearly reached statistical significance. There was little evidence for a trend of decreasing risk with continuous distance, both for study areas 1-20 and 1-15 combined. Adjustment for maternal age, the main risk factor for chromosomal anomalies, tended to increase odds ratio estimates (see also section 5.1.2.2).

A large proportion of chromosomal anomalies are trisomies of all or part of a specific chromosome (Angell et al, 1994). Trisomies result in the majority of cases from non-disjunction of two paired chromosomes during the meiotic division of germ cells (Angell et al, 1994; Sherman et al, 1991). Examples are trisomy of chromosome 21 (Down syndrome), trisomy 18 (Edward's syndrome), and trisomy 13 (Patau's syndrome). Other, non-trisomy, chromosomal anomalies may result from breakages and subsequent rearrangements of pieces of chromosomes in germ cells. Chemical agents have been shown to induce chromosomal breakages and non-disjunction in experimental studies (Adler and Parry, 1993; Allen et al, 1986; Bond and Chandley, 1983; Malling and Wassom, 1977). Chemicals found to induce aneuploidy (fewer or more chromosomes than normal) in experimental studies include certain pesticides and heavy metals (Bond and Chandley, 1983). Very few studies have investigated links between environmental exposures and risk of chromosomal congenital anomalies in humans. Down syndrome has been studied in relation to exposure to diagnostic X-rays (Bell, 1991; Bond and Chandley, 1983; Strigini et al, 1990), low dose environmental ionising radiation (Bound et al, 1995; Little, 1993), smoking (see also section 2.5.5) (Chen et al, 1999; Cuckle et al, 1990; Hook and Cross, 1985; Hook and Cross, 1988; Kallen, 1997), fluoride in drinking water (Bell, 1991; Erickson, 1980; Needleman et al, 1974),

and certain occupational exposures (Olshan et al, 1989). For none of these exposures strong evidence for causal relationships exists (Bell, 1991). Previous landfill studies have generally not studied chromosomal anomalies separately from non-chromosomal anomalies (Goldman et al, 1985; Shaw et al, 1992; Sosniak et al, 1994), or not included chromosomal anomalies in their data (Croen et al, 1997; Marshall et al, 1997). One study that did study chromosomal anomalies, found a statistically significant increase in risk of chromosomal anomalies specifically related to landfill sites containing plastics (Geschwind et al, 1992).

Studies of exposures in relation to chromosomal anomalies are hampered generally by the fact that an unknown, but probably large, proportion of cases of chromosomal anomaly result in spontaneous abortions very early in pregnancy (Kline et al, 1989). This study included cases which were spontaneous abortions from a gestational age of 20 weeks. A large number of cases of chromosomal anomaly could still have been missed however. In one centre, Slovenia, only live born cases of Down syndrome were included and results for this centre (study areas 16 and 17) must be interpreted with great caution.

The odds ratio estimates found for chromosomal anomalies (1.41 for study area 1-15) were similar to those found for non-chromosomal anomalies (1.33 for study area 1-15), but based on a smaller number of cases and not statistically significant. The similarity in risk estimates is difficult to interpret. Although landfill exposures may contain chemicals which have the potential to cause both abnormalities in chromosomes in parental germ cells before conception and developmental abnormalities in the embryo, it seems unlikely that exposures would lead to the *same* magnitude increase in risk of both non-chromosomal and chromosomal malformations. Alternative explanations are that the similar pattern is due to chance, to an unknown systematic error in exposure measurement, case selection, or control selection, or to an unknown, unmeasured confounding effect.

5.1.4.4 Malformation subgroups

Results show statistically significant excesses in risk of neural tube defects, malformations of the cardiac septa, and anomalies of the great arteries and veins, and excess risks of borderline significance for tracheo-oesophageal anomalies, gastroschisis, and hypospadias. Most other malformation subgroups also showed increases in risk but these did not reach statistical significance.

From the literature (see also sections 2.3 and 2.4) it is not possible to derive strong a-priori hypotheses about which anomalies could be expected to show greater risk in relation to residence near landfill sites, or in relation to specific chemical exposures or chemical mixtures. Previous landfill studies which have studied malformation groups have either studied a range of major structural defects (Geschwind et al, 1992; Shaw et al, 1992) or a few selected subgroups (Croen et al, 1997; Marshall et al, 1997). In these studies central nervous system defects (Geschwind et al, 1992), neural tube defects (Croen et al, 1997), musculoskeletal defects (Geschwind et al, 1992), defects of the integument (Geschwind et al, 1992), and cardiac defects (Croen et al, 1997; Shaw et al, 1992) have shown increased risks near hazardous waste sites, although these increases were not always statistically significant (Croen et al, 1997). Since most of the specific relationships have been reported in one or two studies only, they did not greatly inform a priori hypotheses for this study. Cardiac defects and neural tube defects, the main malformation subgroups showing an increased risk in this study, have repeatedly been linked to various other environmental and occupational exposures (see chapter 2.3). These defects are also some of the most common groups of congenital anomalies, and are therefore both more likely to be studied than less frequent anomalies and more likely to reach statistical significance in epidemiologic studies, including the present study. Also, because more than 20 malformation subgroups were tested, chance may have led to at least one of the odds ratios being statistically significant at a 5% significance level. For these reasons, results for malformation subgroups in this study should be interpreted with caution and used mainly to inform hypotheses in further studies.

Although only tentative conclusions can be drawn, the finding of increased risk of certain cardiac defects in this study may be of interest since cardiac defects have been reported in several previous studies to be related to exposure to solvents in drinking water (Bove et al, 1995; Shaw et al, 1990; Swan et al, 1989), and to occupational solvent exposures (Ferencz et al, 1997; Tikkanen and Heinonen, 1992, Correa-Villasenor, 1991 #1488; Wilson et al, 1998). The exposures of most concern in relation to landfill sites, although based on little very study, have been solvents in water and VOCs (many of which also fall under the family of organic solvents) in landfill gas (section 2.2). The increase in risk of hypospadias is of particular recent interest in the light of hypotheses that male reproductive abnormalities, including hypospadias, may be linked to endocrine disrupting chemicals such as PCBs, dioxins, and certain pesticides (Toppari et al, 1996).

5.1.4.5 Differences between landfill sites

It would be important to know whether increased risk of congenital anomaly, if any, is related to all types of landfill sites, or to sites with certain characteristics specifically. In this study, excess risks of non-chromosomal and chromosomal anomalies are found near landfill sites in some study areas but not in others. Statistical tests of heterogeneity of odds ratios between study areas showed no evidence for the risk of congenital anomaly to differ between sites, although such tests have limited statistical power (section 3.7.2).

Analyses did not differentiate between sites by specific individual site characteristics such as age, size, and country where the site is located, although such differentiations were suggested to us after publication of the first results of the study by professionals in the fields of landfill and public health. Firstly, it is not possible from what is currently known about factors influencing hazard potential of sites (section 2.1), or from previous epidemiologic studies of landfill sites (section 2.4), to select one or a few factors with strong a-priori hypotheses that they are, each individually, strong determinants of hazard potential. Analysis of a large number of individual site characteristics without a-priori hypotheses, would lead to obvious interpretational problems. Instead, sites were classified according to their hazard potential *combining* information on many site characteristics, including age, size, and management of sites, into a hazard potential scoring, as discussed in section 5.2.

The study included both open and closed sites which ranged from old uncontrolled dumps to relatively modern controlled operations. From a landfill regulation policy point of view it would be of interest to group sites that are 'similar' according to their management practices and pollution controls. However, problems in interpreting differences between 'old' sites (those without modern controls) and 'modern' sites (those with stricter controls) are evident: they could be due to differences in controls or to differences in time allowed for contamination, if any, to build up in their vicinity. A current 'modern' site may in 30 years' time pose similar hazards to a current 'old' site.

It would be interesting also to link risk of congenital anomalies or specific malformation subgroups to specific chemical emissions from sites. Some of the previous U.S. multi-site studies have carried out analyses by types of chemicals dumped at sites, classifying sites into 'solvents', 'heavy metals', and 'pesticides' for example (Croen et al, 1997; Geschwind et al, 1992; Marshall et al, 1997; Shaw et al, 1992). Information on types of chemicals deposited at the EUROHAZCON study sites was not available in enough detail to permit this type of analysis. Also, the vast majority of sites included in the study took a mixtures of

chemicals and a categorisation into specific chemical subgroups would probably not result in great differentiation between sites. Moreover, classifying sites by types of chemicals dumped may not be a very good predictor of the types of chemicals to which residents near sites might be exposed, since the composition of wastes entering a site may bear very little resemblance to that of trace contaminants present in leachate and landfill gas emissions from sites (section 2.1).

Twenty six hazardous waste landfill sites were selected for this study in eleven European regions covered by the participating malformation registries. In total, thousands of closed and operational landfill sites are located in Europe. It is not possible at this stage to conclude whether findings for this set of study sites, if causal, can be extrapolated to all hazardous waste landfill sites in Europe, or possibly even to any other type of landfill site. Municipal waste sites for example are numerous and may entail similar hazards to designated hazardous waste sites (section 2.1.2.1). Future study will need to investigate other sites, landfills as well as other industrial sites, to place the current findings into context.

5.2 RISK OF CONGENITAL ANOMALY IN RELATION TO HAZARD POTENTIAL OF LANDFILL SITES

A panel of four experts scored the relative hazard potential of landfill sites included in the EUROHAZCON study on the basis of available information on sites collected in questionnaires (section 3.6.2 and 4.3). The expert panel hazard scoring was used to examine whether sites classified as posing a greater hazard were those with greater relative risk of congenital anomaly nearby (section 4.4). There was little evidence for relative risk of congenital anomaly close to (within 3 km of) landfill sites to be associated with the hazard potential of landfill sites as assessed by the expert panel scoring. For non-chromosomal anomalies, data showed a statistically significant increase in relative risk close to sites with increasing hazard posed by sites in the water hazard classification. No evidence for such a trend was found for overall or air hazard of sites for non-chromosomal or chromosomal anomalies. Anomalies of the cardiac septa and chromosomal anomalies showed some evidence, although not statistically significant, for an increase in risk with increasing water hazard. Similarly risk of neural tube defects increased with increasing air hazard, although again this trend was not statistically significant. A large number of uncertainties play a role in the hazard scoring and classification and results should be interpreted with extreme caution.

The following sections discuss these uncertainties before interpretation of the findings is discussed in section 5.2.2.

5.2.1 Expert panel scoring methodology

An important question in interpreting results from the hazard potential classification is whether the classification accurately reflects the true relative hazard posed by study sites, i.e. whether it is a valid measure of the relative hazard potential of sites. Verification of the hazard potential classification, for example by environmental monitoring data or by direct measurements of exposure of residents, was not possible in this study. Routine environmental monitoring data were not readily available for all sites and were not easily comparable between sites (section 4.3.1). The study had no resources to carry out environmental sampling or monitoring of exposure in residents. The absence of a 'Gold-Standard' for verification of the scoring makes evaluation of its validity difficult.

The hazard classification was based on subjective assessments by specialists working as regulators/inspectors or as operators of landfill sites. Expert panels have not been used commonly to assess environmental hazards in general and landfill sites in particular, but they have been proven useful in occupational settings to estimate exposures from job descriptions and job titles where direct exposure measurements were not available (de Cock et al, 1996; Goldberg et al, 1986; Rybicki et al, 1998; Teschke et al, 1989). Expert panel assessments, so-called 'Delphi-techniques', have also been used extensively to underpin decision making processes in health services, for example to assess treatment and care practices (Fiander and Burns, 1998; Gale et al, 1998).

Previous epidemiologic studies of hazardous waste sites in the U.S. have used more formalised, systematic scoring systems for hazard ranking of waste sites, developed usually as part of larger site assessment programmes such as the Superfund clean-up programme (Croen and Shaw, 1996; Geschwind et al, 1992; Marshall et al, 1997). As discussed in section 3.6.2, these ranking systems were not suitable for use in this study mainly because they required more detailed site information than was available. Systematic information, particularly on waste inputs, is generally not available for landfill sites in Europe. This has been noted also by a recent report evaluating the use of a risk assessment tool on two U.S. and three U.K. landfill sites, which concluded that "in the U.K. it is not possible to characterise the majority of landfills even to the level where a simple risk assessment

framework can be employed on a site-specific basis. This particularly applies to the characterisation of emplaced waste" (Department of the Environment, 1994).

In any case, little is known in the published literature about the validity of existing U.S. ranking systems, even of well-used systems such as the U.S.EPA Hazard Ranking System.

In addition to the expert panel scoring, an adaptation of one existing systematic ranking methodology (JRB Associates, 1982) was assessed for use in this study (Appendix 8). This system correlated reasonably well with the expert panel scoring for overall and water hazard scoring, whereas correlation between the two scoring methods was minimal for air hazard scoring. The expert panel scoring was judged more valid than the systematic scoring system for use in this study (section 3.6.2 and Appendix 8), which is why the expert panel scoring was chosen for final classification of sites. The four experts on the EUROHAZCON panel felt that scoring of the hazard potential of the sites relative to each other had been possible on the basis of the information provided, although this assessment is entirely subjective and cannot be verified.

5.2.1.1 Misclassification of hazard potential

In the expert panel scoring, misclassification of the hazard potential of sites may have occurred for several reasons. Firstly, as discussed previously (section 2.1), although it is known to some extent which factors may play a role in influencing hazard potential, it is difficult to predict how different factors interlink to determine hazard potential. Lack of ability to predict complex interrelationships between factors may hamper all assessments, systematic ranking systems as well as expert panel assessments.

In addition, lack of information may have limited the accuracy of the experts' scoring. Landfill questionnaires gave reasonably complete information on site characteristics such as size, age, engineering and management practices (section 4.3.1), but there was little documented data on actual waste types deposited and off-site migration of substances from the sites. Also, some items which may have been of importance were not included in the questionnaire because they were not regarded 'easily obtainable'. For example, the questionnaire did not include information on the direction of the groundwater flow. This is important information in judging whether nearby water wells may be affected by groundwater contamination. At one of the sites, first-hand knowledge from one of the experts led other experts to change their score because nearby drinking water wells were located away from the path of the groundwater flow from the waste sites. The experts indicated that direction of the

groundwater flow and more detailed information on waste types were the main missing items in the questionnaire. Also, they found that in the absence of information on types of waste present, more information on the amount or proportion of biodegradable wastes present in sites, would have been useful to judge its potential to generate landfill gas.

From the above example on changes of scores through first-hand knowledge it may be concluded that the hazard potential of sites for which *no* first-hand knowledge was available, was more likely to be misclassified. However, if one experts had a large interest in how a site was classified, it is conceivable also that first-hand knowledge might, knowingly or unknowingly, have misdirected other experts and led to less accurate site classification. The experts were not aware of the findings regarding risk of congenital anomalies near each site at the time the scoring was performed, and mostly worked for independent site regulators rather than site operators. The expert who worked for a landfill operation company was not involved in the operation of any of the study sites.

Misclassification due to lack of data could have resulted in either over or underestimation of the true relative hazard of sites. In the example above, absence of first-hand knowledge on the flow direction of the groundwater, would have led to an overestimation of the hazard of this site. On the other hand, it is conceivable that a site where contamination is present, but not recorded due to lack of monitoring, may be judged of lower hazard than a site where intensive site investigations and monitoring have shown some contamination. A study of the U.S.EPA Hazard Ranking System for example, showed that in that particular scoring system extra information on sites usually led to a higher hazard scoring (Haness and Warwick, 1991) (section 2.1).

It was difficult to classify the hazard potential of study areas containing multiple sites with differing hazard potential scores. As described in section 3.7.3.2 scores were averaged when 3 km zones around multiple sites in an area were not overlapping, and the score of the highest scoring site taken if 3 km zones did overlap. Experts saw this as the best option but were not confident about assessing hazards from multiple sites, and the possibility that sites in multiple site areas were misclassified can not be excluded.

Twenty one sites in 15 study areas were included in the hazard potential classification. High, medium and low hazard categories therefore contained only 5 study areas each. If misclassification of hazard potential of one or a few sites occurred this will have had a great effect on results regarding the risk of congenital anomaly risk near sites in each hazard category, especially if sites in the more densely populated study areas were misclassified.

Some of the multiple site areas (13 and 15) were also the areas with the largest numbers of cases and controls and their classification as either low, medium, or high hazard, will have made large impact on the odds ratio estimates calculated for each hazard category.

5.2.1.2 Reliability

An assessment of the reliability of a classification can be useful in assessing its validity, i.e. how likely the classification is to accurately measure what it is intended to measure. If the reliability of a classification instrument is high then it is possible, but by no means certain, that the instrument has a high validity (Fleiss, 1981). On the other hand, low reliability means that the validity of the instrument is seriously questionable. Where classifications are based on the assessment of multiple raters, in this study the expert panel, the agreement between experts on a panel can be assessed to give some indication of the reliability of the method.

The agreement between experts in this study measured by the inter-class correlation coefficient ranged, for the final hazard scoring, from 0.53 (for air hazard) to 0.62 (for overall and water hazard). Values of inter-rater agreement between 0.40 and 0.75 have been reported as fair to good, values above 0.75 as excellent and values below 0.40 as poor (Benke et al, 1997). Inter-rater agreements reported in occupational studies rarely exceed the value of 0.7 (Benke et al, 1997). The agreement found in this study falls within the range of inter-rater agreements reported for example in studies of pesticide applicants (0.4-0.8,(de Cock et al, 1996)), exposures of sawmill workers (0.40-0.68,(Teschke et al, 1989)), workers in various manufacturing industries (0.5-0.7, (Goldberg et al, 1986)), and is higher than found in expert panels assessing metal exposures (0.2-0.5, (Rybicki et al, 1998)) and various occupational chemical exposures (0-0.6, (Benke et al, 1997)). Comparisons may be problematic of course, since different methods for expert assessment have been applied in these different studies.

In the present study, the meeting in which experts discussed differences and reached consensus on scoring was considered especially valuable for improving agreement between experts.

The reliability of the average score calculated from individual experts scores depends not only on the agreement between experts, but also on the number of experts on a panel (Fleiss, 1981; Streiner and Norman, 1989). In general, the more experts on a panel, the more repeatable, and therefore reliable, the average score will be. The expert panel in this

study consisted of four experts, and this number resulted in relatively high values of the average-score-reliability (between 0.82 and 0.86). Some overestimation of the 'average-score-reliability' may have occurred due to final scores of experts not being independent (see also section 3.7.3.1).

Agreement for air hazard scoring was noticeably worse than for water and overall hazard scoring, especially in the initial expert scores. Inter-expert agreement was 0.21 for initial air hazard scores. Changes made at the expert panel meeting improved this to 0.53. The air hazard scoring also showed a very low correlation between scores of the adapted JRB ranking system and the expert panel scores (Appendix 8). Low agreement in the air hazard potential scoring may be due to limited expert knowledge on what determines air emissions from landfill sites, to lack of data included in the ranking questionnaire on factors that determine air hazard, and to differences in how experts dealt with missing information. The questionnaire information included relatively complete information on most factors known to influence air emissions such as gas collection, capping and covering of a site. Data on migration of landfill gas were largely lacking however (only available for 43% of sites) and experts indicated that some estimate of the amount of biodegradable waste present in sites would have been useful in assessing landfill gas generation.

5.2.2 Interpretation of findings

5.2.2.1 Overall hazard

The overall hazard scoring of waste sites aimed to capture the total relative hazard of sites, combining exposures from all possible pathways, whereas water and air hazard scoring aimed to reflect contamination hazards via each of the two main exposure pathways separately. If residence near landfill sites is causally related to congenital malformation, greater relative risks would be expected near sites with greater overall hazard, and, depending on the most likely pathway of exposure, with greater air or water hazard. Assuming a high accuracy of the overall, water and air hazard scoring, one would expect a relationship between *overall* hazard of sites and congenital anomaly risk to add more weight to evidence for residence near waste sites being causally related to risk of congenital anomalies, than a relationship with *water* or *air* hazard alone.

Analyses of anomaly risk near waste sites by overall hazard category (low, medium, high), and continuous hazard score suggested no trend of increasing risk near sites with increasing hazard potential scoring for non-chromosomal anomalies, chromosomal anomalies, or selected malformation subgroups (neural tube defects, malformations of the cardiac septa, anomalies of great arteries and veins). These findings, if they represent true absence of a relationship, do not support evidence for causality of an association between distance of residence from hazardous waste landfill sites and risk of congenital anomaly as described in section 5.1.

However, extreme caution is warranted in drawing this conclusion because of problems in the hazard scoring noted in the previous section (5.2.1). As discussed, misclassification of hazard potential of sites is likely to have occurred. The extent of such misclassification can not be estimated due to lack of a 'gold-standard'. Misclassification of sites, if not related to the risk-status of a site (i.e. the relative risk of congenital anomaly nearby the site compared to further away), would usually have led to a dilution of a possible relationship between relative risk near sites and hazard potential. Some systematic bias may have occurred for example where lack of data on site characteristics has led to over or underestimation of the hazard potential of a site (see also section 5.2.1.1). Sites with little available data are more likely to be misclassified and may also be sites with less pollution controls and therefore higher risks of congenital anomaly may occur nearby these sites. This type of bias may have led to both an over and underestimation of the strength of any true relationship.

The power of this study to detect differences between landfill sites is limited (see also section 5.1.4.5). The statistical test of interaction between the risk of congenital anomaly in relation to distance from sites and the hazard potential score or classification of sites has limited power, as do interaction tests in more general (Pocock, 1993; Thompson, 1995). The absence of a relationship with overall hazard seems unlikely to be due to lack of statistical power however: neither hazard category or continuous hazard scoring analyses showed evidence of increasing odds ratios with increasing hazard (chapter 4.4.1).

It is at this stage not possible to conclude with any certainty whether the absence of a relationship between risk of congenital anomaly near sites and overall hazard potential found in this study, occurred because the expert panel scoring method was not able to adequately distinguish hazard potential of sites, or because no causal relationship exists between residence near sites and congenital anomaly risk.

5.2.2.2 Water hazard

The water hazard score reflects the relative hazard posed by a site through the water exposure pathway. Factors such as measures taken to limit migration of landfill leachate, soil permeability, depth to groundwater, and presence of drinking water wells, are important in determining water hazard potential (section 2.1). Data show some evidence for a trend of increasing relative risks for congenital anomaly near waste sites with increasing water hazard of sites. This trend was statistically significant for non-chromosomal anomalies when analysing relative risk in three hazard categories (low, medium, high), although not when analysing risk with continuous hazard score. Some evidence of a trend, but not statistically significant, was found for chromosomal anomalies and malformations of cardiac septa.

It is not possible to conclude whether these findings are due to chance, whether they are due to bias (possible overestimation of hazard potential for high risk sites, see previous section), or whether they reflect that water scoring measured the true relative hazard of landfill sites better than overall scoring.

It would not be justifiable to conclude from these results that the water pathway is the most important exposure pathway for sites in this study. Problems with the hazard classification warrant extremely cautious interpretation, as discussed in detail in previous sections. There may be some reason however, to believe that hazards of landfill sites through the water pathway were easier to assess for the experts than air hazards. Factors influencing water hazard may have been better understood, and better predictable from the information available to the experts. The agreement between experts on the water hazard scoring was better than the air hazard scoring and correlated better with the adapted hazard ranking system.

5.2.2.3 Air hazard

The air hazard scoring aimed to reflect the relative hazard posed by study sites to cause emission of toxic chemicals into the air in gaseous form or bound to dust and particles. There was no evidence for a trend of increasing congenital anomaly risk near landfill sites with increasing air hazard of sites for non-chromosomal anomalies, chromosomal anomalies or two of the three malformation subgroups studied. Only neural tube defects showed some evidence of an increasing relative risk near sites with increasing air hazard, although this trend was not statistically significant. These findings again do not add support to any

conclusions regarding causality of a relationship between residence near waste sites and risk of congenital anomaly. The reliability of the air hazard scoring was not as high as for water and overall hazard scoring and its validity therefore more doubtful.

5.2.2.4 Chromosomal anomalies and malformation subgroups

Patterns of odds ratios by overall, water, and air hazard categories are similar for non-chromosomal anomalies and chromosomal anomalies (comparing Table 4.19 and 4.20). In analogy to the issue raised in section 5.1.4.3, this could indicate that results are due to chance, bias or confounding factors. The hazard analyses are sensitive to the classification of 'large' study areas (areas with large numbers of cases), as discussed in section 5.2.1.1. Some of these larger study areas showed similar increases within 3 km compared to 3-7 km in risk of both non-chromosomal and chromosomal anomalies, although not statistically significant for the latter (areas 13 and 15, see Table 4.6 and 4.7). Classification of such sites may have driven the results of both non-chromosomal and chromosomal anomalies, leading to similar patterns whether they represent 'true' patterns or are due to chance and/or bias.

Interestingly, malformation subgroups analysed in relation to the hazard potential classification showed different patterns of risk with hazard potential: neural tube defects showed some evidence of a trend with air but not with water hazard, cardiac septal defects showed some evidence of a trend with water but not with air hazard. Although these findings may be due to chance (the trends reported were not statistically significant), they may alternatively indicate risks of different malformations occurring through different possible exposure pathways, possibly through exposures to different substances.

5.2.2.5 Exploratory models of hazard score and continuous distance

Models of an exponentially declining risk best predicted the decline in risk of non-chromosomal anomaly with continuously increasing distance from waste sites (section 4.2.3). Continuous hazard scores were incorporated into this model (section 4.4.2) under the hypothesis that if a causal relationship exists between distance from waste sites and congenital anomaly risk, incorporating the hazard score should improve the prediction of malformation risk in this model. Models incorporating hazard score are exploratory and presented mainly as a possible basis for further development. Results showed that incorporating water hazard score slightly improved the fit of the model, overall hazard scores

did not change the model fit, and air hazard scores very slightly worsened the model fit. This matches the results of risk in dichotomous distance zones by hazard score discussed in the previous sections. Absence of a formal statistical test for the difference in model fits seriously limits interpretation of these findings. Also, the assumption of a linear relationship between hazard score and malformation risk (i.e. each same unit increase in hazard score leads to a same unit increase in relative risk next to a site) is hard to verify. In addition, all previously discussed uncertainties in the hazard scoring (section 5.2.1) play a role. An advantage of the models is that arbitrary cut-offs in distance of residence from the waste sites or in hazard potential score are avoided.

With more attention paid to the above problems, the explorative models presented in this thesis could form a useful basis for development of further continuous distance and hazard score models, specially when problems regarding statistical testing are resolved. Models could be developed for example to incorporate distance of residence from multiple sites and hazard score of multiple sites, and could be integrated with dispersion modelling to take account of directional effects.

5.2.3 Recommendations for hazard potential scoring of landfill sites

Although it is hard to draw strong conclusions from the hazard scoring analyses at this stage, I feel that the expert panel scoring methodology could form a valuable basis for future hazard assessments in epidemiological studies. Expert panel scoring may indeed be one of few feasible methods for hazard classification of landfill sites in epidemiological investigations in Europe, considering the quality of site information that is currently readily available. Some suggestions to improve the method of expert panel scoring as presented in this thesis can be made:

- Questionnaire information should include information not only on whether drinking water wells are located nearby the waste sites but also whether the wells can be contaminated by emissions from the site based on the direction of the groundwater flow.
- Although it is often not possible to obtain detailed information on types of waste deposited at a site, site operators/regulators may be able to estimate the proportion of biodegradable waste present in a site. This may give some better indication of the amount landfill gas produced by a site and therefore of the potential for toxic volatile

trace compounds to be carried with the gas. This would especially be valuable for sites where landfill gas is not monitored.

- Arrangements could be made for experts to visit study sites in addition to providing them with questionnaire information. Site visits would be expected to give experts some better idea of the management of sites and the adequacy of pollution prevention measures, although of the use of site visits should not be overrated. It would be difficult, if not impossible, for experts to assess emissions of toxic chemicals to groundwater or air.
- For each site one person with first-hand knowledge could be included on the panel. Independence of this person to the results of the study and blindness to risk status of the sites would be essential. Depending on the number of sites in a study the size of the panel may become too large for this to be a feasible option.
- An increased number of sites would reduce the sensitivity of results to the classification of individual 'large' sites (sites in densely populated areas). Also, increasing the number of sites would lead to increased power of tests of interaction between hazard category/score and distance from site. Resources permitted, inclusion of a larger number of sites is therefore recommended to improve the usefulness of any future hazard scoring exercise.
- Dispersion modelling using meteorological, topographical, and hydrogeological information may be valuable in mapping patterns of relative exposure around landfill sites and could be combined with hazard potential assessments. Costs of conducting such modelling are relatively limited and could underpin the hazard potential assessments in multiple site areas as well as the definition of distance based exposure zones (see also section 5.1.1).
- Special attention should be paid in future studies to the estimation of joint exposures from multiple sites. Both purely distance based analyses and the assignment of hazard scores to multiple site areas could be improved by improved modelling of multiple site exposures, possibly underpinned by information from dispersion modelling.

5.3 SOCIO-ECONOMIC VARIATION IN RISK OF CONGENITAL ANOMALIES

Data presented in section 4.5 show socio-economic variation in the risk of congenital anomalies of non-chromosomal origin and some specific anomalies, with an overall 40% excess (95% CI 4%-91%) in the most deprived areas compared to the most affluent areas. According to these figures, if the whole population could achieve the health experience of the most affluent quintile, 18% of congenital anomalies of non-chromosomal origin might be avoided. As was discussed in section 2.5.1, studies using individual social class based on parental occupation have shown risk ratios of up to 1.6 for the highest compared to the lowest social classes (Knox and Lancashire, 1991; Olsen and Frische, 1993). Area-based deprivation (using the Carstairs index) can reveal inequalities in low birthweight as large, if not larger than social class based on individual parental occupation (Pattenden et al, 1999). Risk ratios for the most deprived compared to the most affluent quintiles of the Carstairs deprivation index range from 1.4 for neonatal mortality and 1.6 for stillbirths and low birthweight, to 2.0 for postneonatal mortality and 2.2 for sudden infant deaths (Dolk et al, 1999; Pattenden et al, 1999). Congenital anomalies as a whole thus appear to be among the less socio-economically determined of the various perinatal and infant outcomes.

Results show a more than two fold increase in risk of Down syndrome and all chromosomal anomalies combined in the most affluent compared to the most deprived areas in analyses unadjusted for confounding factors. 30% of cases of chromosomal anomaly had mothers resident in more affluent areas (deprivation quintile 1 and 2), compared to 18% of cases of non-chromosomal origin. After maternal age adjustment, a weak, non statistically significant, trend of increasing risk with increasing affluence remains for chromosomal anomalies after maternal age adjustment (OR 0.73, 95%CI 0.44-1.21). A previous study in Glasgow also found that controlling for maternal age weakened but did not completely annul an trend of higher risk in more affluent areas (Lopez et al, 1995). The finding of a higher risk in more affluent populations, adjusting for maternal age, may result from socioeconomically related environmental exposures differentially affecting intra-uterine survival of fetuses with chromosomal anomalies (Hook and Cross, 1988). This finding could also result if pregnant women in more affluent areas were offered or underwent more prenatal screening for Down syndrome. This would artificially inflate their apparent risk by counting among terminations cases who would otherwise have resulted in unregistered spontaneous abortions. However, there is no evidence for this when data were examined for socio-economic variation in the number of chromosomal and Down syndrome cases that were terminations of pregnancy, adjusting for maternal age (Table 5.2).

Table 5.2: Terminations of pregnancy for chromosomal anomalies by deprivation quintile - U.K. centres

Depr. quint	*TOP*	*SB + LB*	*OR**	*95% CI*	*OR** maternal age adjusted*	*95% CI*
All chromosomal anomalies						
1 (affluent)	12	18	2.92	0.95 - 8.99	1.10	0.31 - 3.92
2	7	21	1.06	0.34 - 3.30	0.79	0.23 - 2.77
3	14	25	1.81	0.64 - 5.14	1.17	0.37 - 3.74
4	8	29	0.87	0.29 - 2.56	0.89	0.27 - 2.92
5 (deprived)	13	44	1.00		1.00	
			p for trend = 0.09		p for trend=0.99	
Down Syndrome						
1 (affluent)	6	15	1.72	0.40 - 7.29	0.53	0.08 - 3.56
2	5	16	1.46	0.38 - 5.63	1.14	0.22 - 6.00
3	10	18	2.44	0.71 - 8.42	2.27	0.41 - 12.43
4	6	22	1.32	0.37 - 4.72	3.25	0.59 - 17.96
5 (deprived)	7	34	1.00		1.00	
			p for trend = 0.42		p for trend=0.46	

TOP = terminations of pregnancy, SB = stillbirths, LB = live births

* adjusted for region and year of birth

** adjusted for region, year of birth, and maternal age

Numbers of cases for malformation sub-group analyses were small and only tentative conclusions can be drawn from these results. However, the strong socio-economic gradient found for cardiac septal defects, with a nearly 3-fold increase in risk in the most deprived compared to the most affluent populations, should be noted. Socio-economic trends of higher risks in lower social classes have been reported in the literature for congenital heart disease(Knox and Lancashire, 1991), ventricular septum defects (Olshan et al, 1991), and some specific cardiac defects (Correa-Villasenor et al, 1991). There are suggestions that a range of environmental risk factors, including maternal illnesses, drug use, and exposure to solvents, may be important in the aetiology of cardiac defects (Ferencz et al, 1997), and further research is clearly indicated. In the current data, digestive system defects also show a strong trend of increasing risk with increasing deprivation although confidence intervals are wide. Knox and Lancashire (1991) report no socio-economic variation for anal atresia which forms 27% of the group of digestive system defects in this study, and to my knowledge there are no other studies of this group, which also includes anomalies of the small intestine, large intestine, liver, gal bladder, and stomach. The 2.5-fold risk increase of borderline statistical significance found for multiply malformed infants in more deprived populations is of interest since most known teratogens cause multiple rather then isolated malformations(Dolk and de Wals, 1992). No other studies have reported on socio-economic variation in multiple congenital anomalies. Oral clefts, both cleft palate and cleft lip, showed no variation with deprivation this study, whereas other reports have been fairly consistent in reporting higher prevalences in lower social classes for oral clefts, particularly for cleft palate (Hemminki et al,

1980; Knox and Lancashire, 1991; Olshan et al, 1991; Womersley and Stone, 1987) (section 2.5.2).

Data suggest only a very slight gradient of increasing risk with increasing deprivation for neural tube defects, if any, although confidence intervals again are wide. Social class has been a well-documented risk factor for these defects, as discussed in section 2.5. There has been little recent study however, and further research in recent time periods is recommended. This could be particularly important in evaluating the impact periconceptional folate supplementation recommendations may have in either increasing or decreasing socio-economic inequalities in prevalence of neural tube defects (Achenson, 1998; De Walle et al, 1998; McDonnell et al, 1999).

Data used to analyse socio-economic variation in risk of congenital anomalies had limited geographical coverage since it was based on study areas around landfill sites defined for the EUROHAZCON project. It is unlikely however that the findings are confounded by the presence of landfill sites in these study areas even though a relationship between proximity to landfill sites and risk of congenital anomalies has been found in the these data (section 4.2). Data indicate that populations living close to landfill sites in the U.K. study areas were less deprived than those living further away: the percentage of controls living in more deprived areas (deprivation quintile 4 and 5) was lower close to landfill sites in the U.K. study areas than further away (0-3 km: 57%; 3-7 km 64%; χ^2=6.8, p=0.009). Adjustment for proximity to waste sites did not result in any substantial change in odds ratios.

In conclusion, the findings, although based on limited numbers of cases and geographical coverage, suggest that risk factors linked to socio-economic status may play a role in some but not other malformations. Risk factors which could mediate the impact of socio-economic status on the prevalence of congenital anomalies include nutritional factors, life-style, environmental and occupational exposures, access to and use of health services, parity and maternal age, and ethnic origin. In order to close the gap in our knowledge the extent of socio-economic differentials in the prevalence of congenital anomalies exist and how they can be explained, the current findings require follow-up in larger studies.

5.4 CONCLUSIONS AND FURTHER RESEARCH NEEDS

5.4.1 Conclusions

This thesis reports results of a first European case-control study of risk of congenital anomaly near twenty six hazardous waste landfill sites in six countries (EUROHAZCON). Risk of congenital anomaly was analysed in relation to distance of residence from landfill sites, in relation to hazard potential classification of landfill sites, and in relation to socio-economic deprivation (an important potential confounding factor in the study). Limitations of this research and interpretation of the results have been discussed in previous sections. The main conclusions that can be drawn from this work can be summarised as follows:

1. A statistically significant 33% excess in risk of non-chromosomal anomalies is found for living close to (within 3 km from) a hazardous waste landfill site compared to living further away (3-7 km). Confounding factors or biases do not readily explain these findings. Data show a steadily declining risk of non-chromosomal anomaly with increasing distance of residence from sites, adding support to a possible causal relationship. Causality cannot however be inferred from one epidemiological study. Evidence from previous epidemiological landfill studies and epidemiological and teratological studies of individual chemical exposures is not sufficient at present to greatly improve the conclusiveness of the present study.

2. The main problem in interpretation of the findings of this study is the absence of evidence that exposure of residents near study sites occurred or that landfill sites in more general cause exposure of nearby residents. Information on the types of chemicals to which residents may be exposed, on the most likely pathways of exposure, or on whether exposure, if any, would exceed threshold doses needed to induce congenital malformations, is largely lacking. Review of the little literature available shows that organic chemicals, solvents in ground and drinking water and volatile organic chemicals in air emissions, have attracted most concern as possible exposures from landfills. Concentrations of these chemicals have reportedly been high in drinking water near certain sites. Concentrations in air have exceeded air quality guidelines in the immediate vicinity of sites but generally dilute very fast as distance from sites increases.

3. The current study had limited power to analyse differences between landfill sites. Study sites were selected on the basis of their intake of 'hazardous' waste of non-domestic origin, but varied hugely in their size, age, design and management. This disparity makes it difficult at this stage to conclude, if indeed the association is causal, whether risks are related to landfill sites in general or whether specific types of sites may be posing a risk. Also, the study sites represent only a small sample of all hazardous waste landfill sites located in Europe and further research of other landfills, hazardous and municipal, is needed to put the current results into context.

4. If the association reported for non-chromosomal anomalies is causal, 25% of congenital anomaly cases or 2 per 1,000 births, are estimated to occur in excess of the expected prevalence within 3 km of hazardous waste landfill sites. A small percentage (estimated less than 3%) of all congenital anomaly cases in the general population might be avoided if all exposure to contamination from hazardous waste landfill sites was prevented, again assuming causality.

5. Data suggest an increase risk near hazardous waste sites in some specific non-chromosomal anomaly groups: neural tube defects, malformations of the cardiac septa, anomalies of the great arteries and veins, tracheo-oesophageal defects, gastroschisis, and hypospadias. Only very tentative conclusions can be drawn since no strong a-priori hypotheses exist for any of these malformation groups. Findings should be used mainly to inform further study.

6. There was little evidence for an association between risk of chromosomal anomalies, Downs syndrome or non-Downs syndrome, and distance of residence from hazardous waste landfill sites. Chromosomal anomalies show an increase in risk close to waste sites which is similar to that found for non-chromosomal anomalies, but non-statistically significant, and no trend is found of decreasing risk with increasing continuous distance from the sites.

7. A method of expert panel hazard scoring was the most suitable method to classify the hazard potential of EUROHAZCON study sites, considering the quality of readily available information on site characteristics collected through site questionnaires. In the absence of a 'Gold-Standard' for verification of the hazard classification it is not possible to estimate the extent to which the hazard potential of study sites may have been misclassified. Agreement between the four experts seemed reasonably good compared to agreement reported for expert panels in occupational literature, especially for overall

and water hazard scoring. This suggests that the method was reasonably reliable. A meeting in which differences between experts were discussed and consensus were reached was considered valuable in improving the reliability of the scoring.

8. There was little evidence for relative risk of congenital anomaly close to (within 3 km of) landfill sites to be associated with the hazard potential of landfill sites as assessed by the expert panel scoring. Data show some evidence of a trend of increasing relative risk with increasing water hazard of sites, but not with either overall or air hazard. These findings add little support to evidence for the relationship between distance from a waste site and risk of congenital anomaly being a causal one. However, misclassification of the hazard potential of sites may have occurred, and interpretation must be extremely cautious.

9. Although it is hard to draw strong conclusions from the hazard scoring analyses at this stage, the expert panel scoring methodology could form a valuable basis for future hazard assessments in epidemiological studies. Recommendations for further work include adding certain items to the site questionnaire, conducting site visits, increasing the number of experts with first-hand knowledge about sites on the panel, increasing the number of landfill sites studied, and modelling of exposure to multiple sites.

10. This thesis identifies an important gap in the literature on variations in risk of congenital anomaly with socio-economic status. Data collected for the purposes of the EUROHAZCON study in U.K. study areas, suggest that more deprived populations have a higher risk of congenital anomalies of non-chromosomal origin (OR 1.4, 95% CI 1.04-1.91) and some specific anomalies: cardiac septal defects, digestive system anomalies, and multiple anomalies. These data are based on limited numbers of cases and limited geographical coverage. Larger studies are needed therefore to confirm these findings and to explore their aetiological implications.

5.4.2 Further research needs

Research into the health effects of landfill sites as well as research into congenital anomaly aetiology is relatively immature, and further research in both areas could improve current understanding. In general, future studies of landfill sites would greatly benefit from a more interdisciplinary approach, drawing from the fields of landfill engineering, environmental sciences, toxicology, and epidemiology. Research in the following general fields would be particularly useful:

- Toxicology and epidemiology of individual chemicals

Improvements in the base of toxicological and epidemiological data on effects of *specific* chemical exposures would improve our understanding of possible risks of the migration of these chemicals from landfill sites into the environment. This thesis showed that data are generally too limited to assess the teratogenic potential of chemical substances commonly present in pollution from landfill sites. Others have concluded that only a small proportion of the thousands of chemicals used today have been adequately tested for reproductive or developmental toxicity (Marcus et al, 1993). Improved data on effects of individual chemical exposures would improve the quality of quantitative risk assessments that can be made for landfill exposures. However, quantitative risk assessments are based to a large extent on unverifiable assumptions, and cannot therefore negate the necessity for direct epidemiological studies of people living near landfill sites.

More research into effects of chemical mixtures and possible interactions between single chemicals is needed to improve understanding of effects of multiple chemical exposures. Such research is complex but new research initiatives are underway, mainly in the U.S. For example the EPA MIXTOX database which contains toxicological data on interactions of hundreds of pairs of chemicals is a promising new development (Teuschler and Hertzberg, 1995). Research developments and future directions in this field are discussed in detail by a number of authors (DeRosa et al, 1996; Johnson and DeRosa, 1995; Teuschler and Hertzberg, 1995).

- Congenital anomalies: environmental risk factors and spatial clustering

In a large percentage of congenital anomalies aetiology remains unknown. In order to put results of studies such as the present one into context, further research is needed on environmental, including socio-economic, risk factors of congenital anomaly. More

specifically, more systematic investigation of congenital anomaly risk near other sources of environmental pollution would be valuable. Also, assessment of the extent to which congenital anomalies tend to cluster in space would provide context to the current findings, as well as to reports of individual clusters of congenital anomalies. If generalised spatial clustering of congenital anomalies occurs, the finding of an excess risk near landfill sites in this study may not be as unusual as suggested by the statistical significance of the results (Dolk et al, 1999) (Appendix 2).

- Epidemiological landfill studies

The investigation of single landfill sites will remain important as a response to community concerns, although interpretation is often limited due to small population sizes and post-hoc statistical testing. More multi-site studies with large study populations should be carried out, in order to draw conclusions about more general risks. Ideally such multi-site studies should attempt to classify sites in such a way that risks related to specific site characteristics can be investigated, in order to improve their usefulness in waste management and landfill regulation policies. As discussed in this thesis, systematic site assessments needed to underpin such classifications are at present totally lacking in Europe. Standardised waste input recording systems and monitoring practices across European countries and the availability of summary reports of waste inputs and monitoring results, would aid site classifications for epidemiological studies as well as exposure assessments and risk assessments. Specific areas of further epidemiological research likely to prove most useful are:

- the study of people with higher exposures: for example children because they come into higher contact with potentially contaminated soil; people who eat local food products; workers at waste sites; people with life-styles, possibly socio-economically determined, which lead to higher exposures (British Medical Association, 1991).
- the study of 'worst case landfills'. In the absence of adequate exposure data it is difficult of course to define worst case sites. It could be argued that identification of 'worst-case' landfills should form part of regulatory practice in Europe. However, in the absence of systematic investigation of this kind, the study of sites where high off-site contamination has been detected and sites which have been subject to less regulation (possibly sites in developing countries or Eastern Europe) could be suitable for the study of 'worst-case' scenarios provided appropriate health data can be collected.
- Before and after comparisons of disease rates near landfill sites. Before-after comparisons have improved interpretation of some previous landfill studies (section 2.4,

(Berry and Bove, 1996; Fielder et al, 1998; Kharrazi et al, 1997). Before and after comparisons will generally be feasible only for sites which started operating within time periods with good quality health data.

- Improvement of exposure assessments

Exposure assessment is the main weakness in epidemiological studies of landfill sites, including the current study. Development of more accurate exposure measurements which are suitable for landfill exposures is therefore important. For example, collaboration between epidemiologists and basic scientists to further develop biomarker techniques for use in studies of environmental exposures is required. Also, dispersion modelling could be further integrated with epidemiological studies to provide information on possible spatial patterns of contamination from landfill sites.

- Risk perception and risk communication

Further research in the area of risk perception and integration of risk perception research in epidemiological studies are needed to improve our understanding of the impact of social factors and risk perceptions on both actual and perceived ill-health in waste site communities (section 2.4).

Communication of findings from landfill studies to the public has been unclear and even misleading in the past (Ozonoff and Boden, 1987). Publication of the first EUROHAZCON results led to great attention and often misinterpretation by the media. More attention should be paid to risk communication in epidemiological studies.

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APPENDIX 1 : Statement of Conjoint Work

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Statement of conjoint work

17 March 1999

Name of Candidate: Martine Vrijheid
Thesis Title : Risk of Congenital Anomaly in relation to Residence near Hazardous Waste Landfill Sites.

This PhD thesis draws data from a collaborative European project, EUROHAZCON. The thesis describes 3 parts of this project: 1) the association between risk and distance to a landfill site, 2) the development of a methodology to assess the hazard potential of landfill sites and analysis of the association between risk and hazard potential, and 3) socio-economic variation in risk of congenital anomalies.

Helen Dolk, my PhD supervisor, was the principal investigator of the project, supervised quality-control and data analysis throughout all parts of the project, and took the lead in design, interpretation, and writing-up for publication of the first part. I collaborated in the development of the study protocol, data interpretation, and drafting of reports and scientific papers relating to the first part, and wrote this up independently for my thesis. I took the lead in the second and third parts of the project, in all their aspects, including design and interpretation, and writing up. I was responsible throughout the whole project for co-ordination of data collection and for data validation. I wrote the literature reviews for all parts of the project and carried out all statistical analyses.

Other members of the EUROHAZCON collaborative group also took part in protocol design, supplied data from participating centres, and advised on the classification of congenital anomaly cases. Ben Armstrong advised on statistical analyses. Landfill experts from various European countries advised on the selection and classification of landfill sites.

Results of the first part of the project have been published (Risk of congenital anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study. H Dolk, M Vrijheid, B Armstrong, L Abramsky, F Bianchi, E Garne, V Nelen, E Robert, JES Scott, R Tenconi. Lancet 1998; 3562: 423-427). Helen Dolk, Ben Armstrong, and myself wrote the first draft of this paper, the other investigators also contributed to writing of the paper.

Martine Vrijheid

Helen Dolk (PhD Supervisor)

APPENDIX 2 : Published Papers

- Dolk H, Vrijheid M, Armstrong B, Abramsky L, Bianchi F, Garne E, Nelen V, Robert E, Scott J, Stone D, Tenconi R. Risk of Congenital Anomalies near Hazardous Waste Landfill Sites in Europe: The EUROHAZCON Study. Lancet 1998. 352: 423-27.

- Dolk H, Vrijheid M, Armstrong B and a EUROHAZCON Working Group. Risk of congenital anomalies near hazardous waste landfill sites in Europe: the EUROHAZCON study. in: Disease Mapping and Risk Assessment for Public Health. Lawson A, Biggeri A, et al (Ed). Wiley & Sons 1999.

- Vrijheid M. Health effects of residence near hazardous waste landfill site – A review of epidemiological literature. Environ Health Perspect 2000. In press. (not bound in this thesis)

- M Vrijheid, H Dolk, D Stone, L Abramsky, E Alberman, J E S Scott. Socio-economic inequalities in risk of congenital anomaly. Arch Dis Child. In press. (not bound in this thesis)

Articles

Risk of congenital anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study

H Dolk, M Vrijheid, B Armstrong, L Abramsky, F Bianchi, E Garne, V Nelen, E Robert, J E S Scott, D Stone, R Tenconi

Summary

Background Waste-disposal sites are a potential hazard to health. This study is a multicentre case-control study of the risk of congenital anomalies associated with residence near hazardous-waste landfill sites in Europe.

Methods We used data from seven regional registers of congenital anomalies in five countries. We studied 1089 livebirths, stillbirths, and terminations of pregnancy with non-chromosomal congenital anomalies and 2366 control births without malformation, whose mothers resided within 7 km of a landfill site; 21 sites were included. A zone within 3 km radius of each site was defined as the "proximate zone" of most likely exposure to teratogens.

Findings Residence within 3 km of a landfill site was associated with a significantly raised risk of congenital anomaly (295 cases/511 controls living 0–3 km from sites, 794/1855 living 3–7 km from sites; combined odds ratio 1·33 [95% CI 1·11–1·59], adjusted for maternal age and socioeconomic status). There was a fairly consistent decrease in risk with distance away from the sites. A significantly raised odds ratio for residence within 3 km of a landfill site was found for neural-tube defects (odds ratio 1·86 [1·24–2·79]), malformations of the cardiac septa (1·49 [1·09–2·04]), and anomalies of great arteries and veins (1·81 [1·02–3·20]). Odds ratios of borderline significance were found for tracheo-oesophageal anomalies (2·25 [0·96–5·26]), hypospadias (1·96 [0·98–3·92]), and gastroschisis (3·19 [0·95–10·77]). There was little evidence of differences in risk between landfill sites but power to detect such differences was low.

Interpretation This study shows a raised risk of congenital anomaly in babies whose mothers live close to landfill sites that handle hazardous chemical wastes, although there is a need for further investigation of whether the association of raised risk of congenital anomaly and residence near landfill sites is a causal one. Apparent differences between malformation subgroups should be interpreted cautiously.

Lancet 1998; **352:** 423–27

See Commentary page 417

Introduction

Waste disposal by landfill is a cause for environmental concern. People who live near landfill sites may be exposed to chemicals released into the air, water, or soil.[1] Air contamination includes off-site migration of gases, dust, and chemicals bound to dust, especially during operation of the site. Local surface water and groundwater can become contaminated, and these may in turn contaminate potable water supplies or water for recreational use. Chemical contamination of air, water, or soil may also affect locally grown and consumed food produce. Thus, a landfill site may be a health risk for local residents and their children. Information on the potential risks to health should aid the future design, location, and operation of landfill sites.

To date, however, there is little epidemiological evidence on which to base health-risk assessments of landfill sites. Studies of pregnancy outcomes among women who live near landfill sites have been done in the USA, including the well-known contamination incident at Love Canal[2,3] and multiple-site assessments.[4–8] Some of these studies show raised risks of congenital anomalies in babies whose mothers live near landfill sites, but no clear pattern of risk has yet emerged. The potential teratogenicity of many of the chemicals dumped in landfill sites, such as heavy metals, pesticides, and solvents, is known, but chemical dose may have to reach a threshold level before significant teratogenic effects appear.

Communities close to waste-disposal sites are concerned about the potential health risk of the sites, and may link local "clusters" of adverse health outcomes to exposure to chemicals from nearby sites. However, even with a random spatial pattern of adverse health outcomes, localised clusters will occur, and distinction of these random clusters from those in which there is a common underlying local cause is difficult. It is desirable to move beyond post-hoc study of clusters, to study of waste-disposal sites specified a priori. We studied whether pregnant women living near landfill sites would be exposed to sufficient chemical doses for there to be any risk of congenital anomalies in their children. We present the first results of a collaborative European study of the risk of congenital anomaly among people living near hazardous-waste landfill sites. These first results concern non-chromosomal congenital anomalies.

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Register centre and study area	Number of landfill sites	Study period	Cases (n=1089)	Controls (n=2366)
Funen County (Denmark)				
1	1	1987–93	19	44
2	1	1986–93	28	68
Western North Thames (UK)				
3	1	1990–93	50	124
4	1	1990–93	10	30
Lyon (France)				
5	1	1990–94	35	78
Antwerp (Belgium)				
6	1	1990–93	73	160
7	3	1990–93	35	82
8	1	1992–93	6	16
Tuscany (Italy)				
9	1	1982–93	60	67
10	1	1982–93	121	138
11	1	1987–93	45	53
Northern Region (UK)				
12	1	1989–93	120	300
13	4	1986–93	296	740
14	1	1990–93	23	58
Glasgow (UK)				
15	2	1990–91	168	408

Table 1: **Background information on cases of congenital anomaly and controls**

Methods

Data collection

We used data from seven research centres in five European countries—Belgium, Denmark, France, Italy, and the UK. The centres maintain regional population-based registers of congenital anomalies that include data on livebirths, stillbirths, and terminations of pregnancy after prenatal diagnosis. Five of these centres are in the EUROCAT network of regional registers of congenital anomalies in Europe—register methods have been described elsewhere.[9–12] Three other centres participated in the study, but two of these only register Down's syndrome (Slovenia, UK), and one had too few people resident within the study area around the landfill site for meaningful data analysis (north-east Italy).

The landfill sites studied were located in areas covered by the registers of congenital anomalies. The sites contained hazardous waste of non-domestic origin, as defined in the EC Directive on Hazardous Waste.[13] We studied 21 suitable landfill sites, of which nine closed before the start of the study period and ten were in operation for more than 20 years before the end of the study period.

An area of 7 km radius around each landfill site defined each study area. Each study area contained a "proximate" zone of 3 km radius from the site within which most exposure to chemical contaminants would occur, according to expert advice. If two or more landfill sites were within 7 km of each other, and the proximate zones nearly overlapped, these study areas were combined as one large study area. If the landfill sites were 7–14 km from each other, any study-area overlap was split along a median line, the study population was allocated to the nearest site, and then each study area was analysed separately. The study period for each study area started when the registration of anomalies started, and after at least 5 years' operation of the nearest landfill site to allow for the time it takes for off-site contamination to occur. The study period ended on Dec 31, 1994, at Lyon, and on Dec 31, 1993, at the other sites.

We searched the registers for routinely registered cases of liveborn children with malformations, malformed fetal deaths of 20 weeks' gestation or later, and terminations of pregnancy after prenatal diagnosis of anomaly. Cases had to be born within the study period, and the mother had to be resident in a study area. Congenital anomalies were those on the EUROHAZCON list, which includes most major birth defects but excludes familial syndromes, neoplasms, metabolic diseases, and minor malformations. Chromosomal anomalies were excluded from the current analysis. Cases of congenital anomaly were further classified into non-exclusive subgroups (a baby could have more than one anomaly) based on EUROCAT subgroups.[9] Cardiac anomalies were classed as follows (with International Classification of Diseases, tenth revision, code): malformations of cardiac chambers and connections (Q20); malformations of cardiac septa (Q21); malformations of cardiac valves and other heart malformations (Q22–Q24); anomalies of great arteries and veins (Q25–Q26, except patent ductus arteriosus). Anomalies were multiple if a baby had two or more apparently unrelated anomalies, including recognised associations. All cases of possible syndromes and sequences were reviewed by the medical geneticists and by paediatric members of the collaborative group, who were not told the place of residence in each case. A baby with multiple anomalies was included both in the component anomaly subgroups and as a single case of multiple anomaly. A baby with a non-familial syndrome was included only in the syndrome subgroup. Recognised sequences were classed only in terms of the primary anomaly.[14] Numbers in any subgroup refer to cases, not to the numbers of anomalies.

For every case, two controls were randomly selected from all children without malformations born (liveborn or stillborn) on the nearest following day in the same study area. Two centres (Northern Region, Glasgow, UK) selected controls as a random sample of all livebirths in the same year of birth as the case. In Tuscany there was only one control per case. Twin-pairs were treated as one outcome, and classed as a case if one or both were malformed. Siblings were classed as separate outcomes.

Study area	0–3 km from site		3–7 km from site		Odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
	Cases	Controls	Cases	Controls		
All study areas	295	511	794	1855	1·37 (1·14–1·63)	1·33 (1·11–1·59)
Single study areas						
1	7	23	12	21	0·49 (0·15–1·63)	0·43 (0·11–1·65)
2	11	25	17	43	1·26 (0·47–3·40)	1·23 (0·41–3·67)
3	25	59	25	65	1·16 (0·60–2·26)	0·76 (0·34–1·69)
4	6	18	4	12	1·12 (0·19–6·42)	0·83 (0·11–6·07)
5	4	14	31	64	0·58 (0·17–1·91)	0·45 (0·13–1·60)
6	18	21	55	139	2·19 (1·08–4·45)	2·08 (0·98–4·41)
7	11	11	24	71	2·92 (1·11–7·70)	3·93 (1·20–12·80)
8	0	1	6	15	0	. .
9	21	15	39	52	2·09 (0·92–4·75)	1·29 (0·48–3·49)
10	17	15	104	123	1·38 (0·65–2·94)	1·40 (0·62–3·15)
11	28	38	17	15	0·65 (0·28–1·52)	0·72 (0·17–2·97)
12	23	50	97	250	1·16 (0·67–2·02)	1·26 (0·71–2·22)
13	64	113	232	627	1·52 (1·08–2·15)	1·50 (1·05–2·13)
14	1	4	22	54	0·63 (0·07–6·16)	0·94 (0·09–9·74)
15	59	104	109	304	1·58 (1·07–2·33)	1·63 (1·09–2·44)

*Adjusted for socioeconomic status and maternal age.

Table 2: **Odds ratios for non-chromosomal congenital anomalies for each study area**

Cases and controls were geographically located with the address or postcode of the mother's place of residence, with an accuracy of 100 m or less. The distance of the mother's place of residence from the nearest landfill site was used as a surrogate measurement of exposure to chemical contaminants from the landfill site.

Socioeconomic status and maternal age were recorded for cases and controls. Socioeconomic status was measured in different ways in each country: as a quintile of a deprivation score based on enumeration-district data in the UK;[15] as one of five social classes of parental occupation in Funen County; as one of five classes of maternal education in Tuscany; as one of five occupation groups in Lyon; and in quintiles of average income in the area of residence in Antwerp. Socioeconomic status was recorded for more than 97% of cases and controls overall, and for more than 86% of the cases and controls in individual regions.

Statistical methods

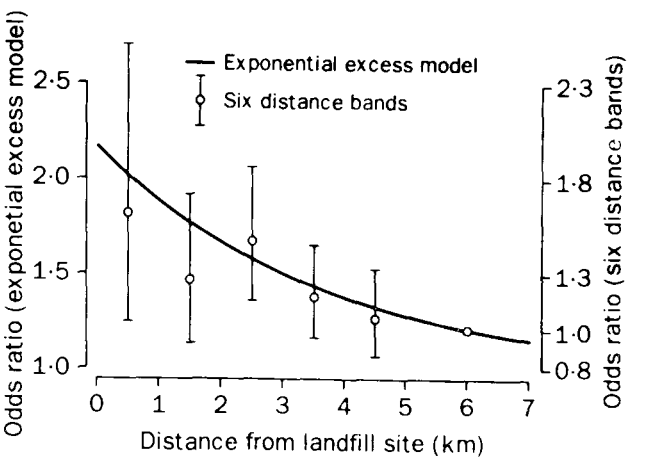
We used logistic and related binomial regression models to investigate the association between residence near hazardous-waste landfill sites and risk of congenital anomaly.[16] All controls, including those selected for cases with chromosomal anomalies, were included in the data analysis, including the subgroup analysis. Case-control matching was not retained in the data analysis, but data were stratified by study area and year of birth. Socioeconomic status was modelled separately for each country because of the different measures used.

Data from all study areas combined were grouped into six distance bands and distance was used as a continuous measure in explicit models. We fitted several models, including one in which the risk of congenital anomaly (odds ratio) declined exponentially with distance from a landfill site.[17] We also fitted various models that allowed for random variation in odds ratios between study areas.[18] We report results from a Bayes random-effects model with a normal distribution of underlying log odds ratios, and "non-informative" gamma (0·001, 0·001) prior for the inverse variance of this normal distribution. Other approaches gave similar results.

Results

We studied 1089 cases of non-chromosomal congenital anomaly and 2366 controls (table 1). We assessed the potential for confounding by maternal age and socioeconomic status. Maternal age had a positive but non-significant relation with risk of congenital anomaly. There was no clear relation between risk of congenital anomaly and socioeconomic status in any of the centres except in the UK, where there was a significant (p=0·04), trend of greater risk of anomaly with increasing deprivation, adjusted for distance from landfill sites (odds ratio for the most deprived quintile relative to the most affluent 1·37 [95% CI 0·98–1·93]). The maternal age and socioeconomic profiles of residents within 3 km of landfill sites and those who lived further away differed within some study areas, but there was no consistent pattern whereby older or more socially deprived people lived closer to landfill sites. Nonetheless, both these variables were included in our statistical models.

The overall odds ratio for congenital anomalies associated with residence within 3 km of a hazardous-waste landfill site, for all study areas combined, adjusted for maternal age and socioeconomic status, was 1·33 (95% CI 1·11–1·59; table 2). Adjustment for confounders did not substantially change the odds-ratio estimates for the combined or for most of the individual study areas. There were four sets of siblings in our sample in which both were malformed, but all lived more than 3 km from landfill sites.



Odds ratios for congenital anomalies with distance from landfill sites

Different scales are needed for the two models because the baseline differs: circle at 6 km represents 5–7 km baseline (odds ratio=1·0, righthand scale) for logistic regression of six distance bands; solid curve at this point represents estimated risk 6 km from site relative to risk infinitely far from site (odds ratio=1·22, lefthand scale).

There was little evidence of heterogeneity in the odds ratios between study areas (p=0·31). Adjusted odds ratios for three of the study areas (7, 13, and 15) were significant (p=0·02, 0·03, 0·02, respectively). The odds ratio for study area 6 was of borderline significance (p=0·05). The lack of evidence of heterogeneity of the odds ratios across study areas was reflected in the Bayes random-effects analysis, the results of which differed little from those of the simple combined analysis (median odds ratio 1·35 [1·07–1·68]).

There was a fairly consistent decrease in risk of congenital anomalies with increasing distance from a landfill site, although CIs in the six distance bands were wide (figure). All models that used distance as a continuous variable fitted our data well, although the exponential-excess model in the figure fitted somewhat better than the logistic models with distance or its reciprocal. All models showed a significant decrease in risk of congenital anomaly with increasing distance from a landfill site (p values ranged from 0·001 to 0·012).

Congenital anomaly	Number of cases	Odds ratio (95% CI)
Neural-tube defects	130	1·86 (1·24–2·79)
Hydrocephaly	32	1·06 (0·44–2·59)
Other central-nervous-system defects	23	1·03 (0·36–2·94)
Malformations of cardiac chambers and connections	45	0·91 (0·42–1·97)
Malformations of cardiac septa	248	1·49 (1·09–2·04)
Malformations of valves and other heart malformations	109	1·17 (0·73–1·88)
Anomalies of great arteries and veins	63	1·81 (1·02–3·20)
Cleft palate	38	1·63 (0·77–3·41)
Cleft lip with or without cleft palate	72	1·18 (0·66–2·12)
Tracheo-oesophageal fistula, oesophageal atresia and stenosis	25	2·25 (0·96–5·26)
Digestive system and upper alimentary tract	59	0·98 (0·49–1·93)
Atresia and stenosis of rectum and anal canal	20	1·02 (0·33–3·15)
Hypospadias	45	1·96 (0·98–3·92)
External genitalia (female + indeterminate)	10	0·89 (0·18–4·53)
Renal abnormalities	75	1·30 (0·73–2·31)
Urinary-tract abnormalities	69	1·14 (0·62–2·11)
Limb reduction defects	41	1·27 (0·61–2·62)
Exomphalos	12	0·26 (0·03–2·19)
Gastroschisis	13	3·19 (0·95–10·77)
Skin and other integument abnormalities	30	1·92 (0·78–4·73)
Syndromes, presumed de-novo mutations	29	1·48 (0·63–3·49)
Multiple anomalies	84	1·21 (0·71–2·06)

Table 3: **Odds ratios for congenital anomalies among residents within 3 km of a hazardous-waste landfill site**

The combined odds ratios for selected subgroups of congenital anomalies among residents within 3 km of a landfill site (table 3) were not changed substantially after adjustment for socioeconomic status and maternal age. Significant unadjusted odds ratios were found only for neural-tube defects (p=0·003), malformations of the cardiac septa (p=0·014), and abnormalities of the great arteries and veins (p=0·041). Odds ratios for tracheo-oesophageal anomalies, hypospadias, and gastroschisis were of borderline signifance (p=0·06). However, there were few cases in most of the subgroups analysed, and thus CIs were wide.

Discussion

We have shown a small, but statistically significant, excess risk of non-chromosomal congenital anomalies among people who live within 3 km of hazardous-waste landfill sites. There is no evidence that the risk of anomalies differs between sites, although our study has limited statistical power to address this issue. The fundamental question is whether the relation observed is causal. In our opinion, the results of previous epidemiological multisite studies[4-6] do not greatly strengthen any conclusion of causality in our study.

Socioeconomic status is the most obvious potential confounder in any spatial analysis of health outcomes. There has been little research on the strength of the relation between socioeconomic status and risk of congenital anomaly.[19-23] Our work suggests a positive relation between non-chromosomal malformations and social deprivation in the UK, but little evidence for the same relation elsewhere in Europe. There was no overall evidence that socioeconomically more deprived communities live near to landfill sites. Moreover, adjustment for socioeconomic status in our statistical analyses, although hampered by the lack of standard socioeconomic classification in Europe, did not greatly change the odds ratios. We therefore think that socioeconomic confounding is unlikely to explain the excess risk of congenital anomaly found near landfill sites.

A second possible confounder is the presence of other industrial sites or toxic environmental exposures near landfill sites. However, there has been little study of the risk of congenital anomaly near any type of industrial site; our results would be of equal interest if the observed association was with other industrial sites, instead of or as well as landfill sites. A further possibility is that mothers resident near landfill sites have jobs with high risks to health, at the landfill site or at other industrial sites. However, it would be unusual for enough of the women in any area to be employed in high-risk industrial occupations for the mean risk of adverse birth outcomes for resident women to be significantly raised.

Congenital anomalies may have been more fully reported close to landfill sites (ascertainment bias). However, the registers used many information sources and active case-finding, they collected data routinely, with no knowledge of the study hypothesis, and an examination of our data by hospital of birth shows that hospital-based ascertainment differences, at least, do not explain the excess risk found near landfill sites.

Women may move house between exposure to potential teratogens and pregnancy outcome, and this can lead to migration bias whereby true excess risk is underestimated. Unlike most chronic effects of exposure to harmful chemicals, teratogenic effects may be detected as early as a few months after exposure to the teratogen. Thus, the potential for migration bias is limited. However, for chemicals that accumulate in the body over time, the length of residence of the mother near the landfill site may be important. There are few estimates of the proportion of mothers who move house during pregnancy, but figures from the UK suggest that about 25% of women move house during pregnancy; of these, about 50% move less than 1 km.[24] We estimate that this migration would lead to roughly a 10% underestimation of any true excess risk of congenital anomaly related to exposures during early pregnancy.[25] There is public concern about the effects on health of several of the landfill sites included in our study. This concern has not, to our knowledge, been specifically related to birth defects, but there may have been more migration in areas close to the landfill sites than is usual because of these health concerns.

Congenital anomalies are heterogeneous in pathogenesis and aetiology, and it would be of interest to investigate whether any particular anomalies are linked to either landfill sites in general or to particular chemicals dumped in them. However, there are no robust a-priori hypotheses about which anomalies occur most commonly around landfill sites, or which anomalies occur after exposure to specific chemicals or chemical mixtures. Furthermore, landfill sites cannot be easily classified according to the chemicals they contain, because each site contains a range of chemicals, and because information on the chemicals dumped is usually incomplete; record keeping has not always been a legal requirement. We have found increased risks of many types of congenital anomaly near the landfill sites, although not all of these findings were significant. There was a significantly overall increased risk of neural-tube defects, malformations of the cardiac septa, and malformations of the great arteries and veins in residents near the landfill sites in our study, and borderline significantly increased risk of tracheo-oesophageal anomalies, hypospadias, and gastroschisis. These findings should be used as hypotheses to inform further study, because no clear interpretation of differences in risk between congenital anomalies can be made. However, increased risk of hypospadias is of particular interest in relation to concern about male reproductive abnormalities related to endocrine-disrupting chemicals.[26]

The environmental hazardousness of a landfill site may be more a result of geology, engineering, and management practices than of the type or amounts of chemicals dumped there.[27] We now aim to rank landfill sites according to "hazard potential" by expert consensus, with concealment of risk status. A "dose-response" effect, in which the sites of highest hazard potential are associated with the highest risk of congenital anomaly, would strengthen the case for a causal association between risk of congenital anomaly and residence near sites. Direct measurement of exposure to chemicals for residents near landfill sites would also help to assess whether the association is causal, but this research has not yet been done.

Our study was limited to landfill sites that handle hazardous industrial wastes. However, municipal landfill sites that take domestic wastes can be as environmentally hazardous as those categorised as hazardous-waste sites,[28] and indeed, in the UK, codisposal (mixture of domestic

and industrial wastes) is recommended. We believe that systematic "environmental health surveillance" is needed for municipal landfill sites and other pollution sources that cause public or scientific concern. Surveillance should make use of the registers of congenital anomaly, should include assessment of people's exposure to chemicals, and should encourage regular communication between departments with health and environment responsibilities. It is unfortunate, for example, that one of the original participants in our study withdrew because the local environment department was unwilling to provide information about the landfill sites in the area covered by the register of congenital anomalies.

Environmental problems cross political boundaries, and a coordinated policy response is necessary, informed by coordinated research. Our results show the need for further investigation of the potential environmental and health risks of landfill sites, and for a more systematic environmental-health surveillance system in Europe.

Contributors

Helen Dolk, Martine Vrijheid, and Ben Armstrong wrote the first draft of the paper. Helen Dolk led the project, designed the study protocol, and supervised quality-control and data analysis. Martine Vrijheid coordinated data collection, did the statistical analysis, and took part in study protocol design. Ben Armstrong supervised the statistical analysis. Leonore Abramsky, Fabrizio Bianchi, Ester Garne, Vera Nelen, Elisabeth Robert, John Scott, David Stone, and Romano Tenconi took part in study protocol design, advised on classification of cases, and supplied data from participating centres. All investigators contributed to writing of the paper.

Acknowledgments

Study coordination was funded by the European Commission DGX11 BIOMED programme Concerted Action Contract BMH1-94-1099. Participating centres were supported by the Fund for Scientific Research (Antwerp, Belgium), GROUPAMA—Assureur Santé (Lyon, France), Northern Region Health Authority (UK), Regione Toscana—UOC Materno-Infantile (Tuscany, Italy), Greater Glasgow Health Board (Glasgow, UK), and the Genetics Purchasing Forum (North Thames, UK). We thank colleagues from collaborating institutions, registers, and the coordinating centre, including Araceli Busby, Jean Chapple, Claire Charmand, Andrena Gordon, Hilary Miller, Anna Pierini, Patrick van Reempts, and Guy Thys; and Giorgio Boschi, Michael Fogh, Torben Jorgensen, Calum MacDonald, Tom McDonald, Isabel Melkebeke, Marco Pelligrini, Patrick Pointer, Fabio Del Soldato, and Réseau Santé-Déchets for expert advice on hazardous-waste landfill.

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29

Congenital Anomalies Near Hazardous Waste Landfill Sites in Europe

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29.1 INTRODUCTION

The EUROHAZCON study is the first European epidemiological study to assess whether the risk of congenital malformation is higher for residents closer to hazardous waste landfill sites than for those farther away.

Waste disposal, whether by landfill or incineration, is one of the foremost environmental concerns today. Knowledge about the potential impact on health is important in deciding on regulation of sites, their siting and remediation. Yet there is little epidemiological evidence on which to base risk assessments. Most studies of pregnancy outcomes among residents near landfill sites have been conducted in North America, from the well-known contamination incident at Love Canal (Vianna and Polan, 1984; Goldman *et al.*, 1985) to more recent assessments around multiple sites (Croen *et al.*, 1997; Geschwind *et al.*, 1992; Marshall *et al.*, 1997; Shaw *et al.*, 1992; Sosniak *et al.*, 1994). Some individual studies have shown raised risks of congenital malformations, but no clear pattern of risk can yet be said to have emerged. There is an extensive literature supporting the potential teratogenicity of many of the chemical classes found in landfill sites (such as heavy metals, pesticides and solvents), but the question is whether nearby residents would be exposed to sufficient doses for there to be any risk, particularly as an individual dose may need to build up to a threshold level for there to be any significant biological effect at all.

Communities close to waste disposal sites are often concerned about the potential health impact, and may link local 'clusters' of adverse health outcomes to exposure to chemicals from nearby sites. Since, even with a random pattern of disease, localised patches of high disease density are bound to occur, it is usually difficult to distinguish

Disease Mapping and Risk Assessment for Public Health. Edited by A.B. Lawson *et al.*

clusters derived from the random disease pattern from those where there is a common underlying local cause. Scientifically, and in order to respond to public concern, it is desirable to move beyond *post hoc* cluster investigations, to investigations around waste disposal sites specified a priori.

Residents may be exposed to chemicals from landfill sites through the air or water (Upton, 1989). The air route includes off-site migration of gases, as well as dust and chemicals adhered to dust, especially during periods of active operation of the site. The water route includes contamination of groundwater and surface water, which may contaminate drinking water if local sources are used, or contaminate water used for recreation or household uses. Contamination of air, water or soil may affect locally grown food produce.

Congenital malformations can be divided into those for which there is a pre conceptional mutagenic basis, whether chromosomal or at the level of a single gene, and those that arise from disturbances of in utero development, usually during the organogenetic period in early pregnancy. In this chapter, we consider non-chromosomal malformations.

29.2 METHODS

This report concerns data from seven centres in five European countries (Belgium, Denmark, France, Italy, UK) (Table 29.1), all of which are high-quality, regional, population-based congenital malformation registers. Five of these centres are part of the EUROCAT network of regional registers for the surveillance of congenital anomalies in Europe (EUROCAT, 1991). Three further centres are participating in the study, but two of these register Down's Syndrome only (in Slovenia and the United Kingdom), and one had too little population within the study area around the landfill site to make data analysis meaningful (North-East Italy).

We identified waste landfill sites, located in regions covered by the participating registers, which contained 'hazardous' waste of non-domestic origin, as defined in the EC Directive on Hazardous Waste (ECC, 1991). The EC list includes chemicals such as heavy metals, solvents, pesticides, dioxins. There were twenty one such hazardous waste landfill sites in all participating regions, of which nine closed before the start of the study period and 10 sites were operational for more than 20 years before the end of the study period.

A 7 km zone around each study site was defined as the study area. Where the study areas of two or more study sites overlapped and the sites were within 7 km of each other, the two (or more) study areas were considered as one large study area. Where the sites with overlapping areas were between 7 km and 14 km from each other, the area of overlap was split in such a way that cases and controls were allocated to the nearest site and each study area was considered separately.

The study period began at the start of the malformation register, or, if later, after five years of operation of the nearest landfill site (to allow time for off-site contamination to occur). It ended 31 December 1993 (31 December 1994 for Lyon).

The cases are registered malformed live births, stillbirths and abortions induced following prenatal diagnosis, born within the study period and to a mother resident in a study area, and having one of the malformations on the EUROHAZCON list. This list includes all major malformations, but excludes familial syndromes, neoplasms, metabolic diseases and minor malformations. Chromosomal anomalies are excluded from the current analysis.

Table 29.1 Total numbers of cases and controls in EUROHAZCON study areas

Centre	Study area	Number of sites	Study period	Cases	Controls
Funen County (Denmark)	1	1	1987–93	19	44
	2	1	1986–93	28	68
North Thames (West) (UK)	3	1	1990–93	50	124
	4	1	1990–93	10	30
Lyon (France)	5	1	1990–94	35	78
Antwerp (Belgium)	6	1	1990–93	73	160
	7	3	1990–93	35	82
	8	1	1992–93	6	16
Tuscany (Italy)	9	1	1982–93	60	67
	10	1	1982–93	121	138
	11	1	1987–93	45	53
Northern Region (UK)	12	1	1989–93	20	300
	13	4	1986–93	296	740
	14	1	1990–93	23	58
Glasgow (UK)	15	2	1990–91	168	408
Total				1089	2366

Controls, two per cases, were randomly selected from all non-malformed live and stillbirths born on the nearest day after the case in the same study area. For convenience, two centres chose to select their controls by taking a random sample from all live births in the same year of birth as the case (Glasgow and Northern Region). In one centre, Tuscany, only one control per case was selected.

Cases and controls were located geographically using addresses or postcodes at birth, with an accuracy of 100 m or less. The distance of residence at birth from the nearest waste site was then used as the surrogate exposure measurement.

29.2.1 Statistical analysis

The association between the proximity to hazardous waste landfill sites and the risk of congenital malformations was investigated using logistic and related binomial regression models (Breslow and Day, 1980). Since individual matching by date of birth was for administrative convenience rather than to control confounding, we carried out an unmatched (unconditional logistic regression) analysis, but included terms for study area and year of birth in all models. The distance from the waste site was first dichotomised into a 0–3 km 'proximate' zone, and a 3–7 km 'distant' zone. These zones were defined a priori on the advice of landfill experts. Information routinely available on

Table 29.2 Odds ratios for maternal age and socio-economic status

	Cases	Controls	OR	95% CI	Trend test *p*-value
Maternal age: all centres					
< 20 years	73	175	0.91	0.68–1.23	
20–24 years	270	615	0.95	0.79–1.15	
25–29 years	391	851	1.00		
30–34 years	232	492	1.02	0.84–1.24	
> 35 years	85	158	1.16	0.87–1.56	0.17
Unknown	38	75			
Socio-economic status					
UK centres: quintiles of small-area deprivation scores					
Affluent: 1	53	167	0.91	0.62–1.34	
2	67	171	1.08	0.75–1.55	
3	100	275	1.00		
4	155	388	1.12	0.84–1.51	
Deprived: 5	290	656	1.25	0.96–1.64	0.04
Unknown	2	3			
Funen County: social class from parental occupation					
High: 1	2	5	1.01	0.17–5.89	
2	2	4	1.22	0.20–7.57	
3	13	33	1.00		
4	18	48	0.95	0.41–2.19	
Low:5	11	20	1.39	0.52–3.69	0.70
Unknown	1	2			
Tuscany: maternal education					
Graduate	8	15	0.58	0.23–1.45	
High School	77	67	1.20	0.76–1.90	
Medium	77	86	1.00		
Elementary	29	56	0.60	0.35–1.04	
None	1	1	1.23	0.08–20.02	0.17
Unknown	34	33			
Lyon: occupational groups					
Professional	1	8	0.20	0.02–1.78	
Intermediate	11	22	0.82	0.31–2.16	
Farmers, craftsmen	4	7	0.98	0.24–3.97	
Workmen	15	26	1.00		
Unemployed	0	8			0.95
Unknown	4	7			
Antwerp: quintiles of average area income					
High income: 1	25	45	1.75	0.81–3.79	
2	23	50	1.73	0.81–3.69	
3	15	58	1.00		
4	21	50	1.59	0.74–3.43	
Low income: 5	28	53	1.84	0.88–3.85	0.92
Unknown	2	2			

socio-economic status (SES) varied greatly between countries participating in the study (Table 29.2). When adjusting for socio-economic status in analyses in which study areas were pooled, SES was therefore separately modelled in each country.

In analyses pooling information over study areas, we analysed the association of risk with distance from a waste site in more detail by grouping more finely and by using distance as a continuous measure in explicit models. As well as standard logistic models in distance and its reciprocal, we fit a model in which excess risk (strictly odds ratio) declines exponentially with distance from the site:

$$\pi/(1-\pi) = \exp(\boldsymbol{\beta}^{\mathrm{T}}\boldsymbol{x})\{1 + \alpha\exp(-\gamma d)\},$$

where π is the probability of being a case, d is the distance from the waste site, and $\boldsymbol{x}$ is a vector of possibly confounding covariates. The parameter γ defines the rate of decline in risk with distance, and α defines the maximum risk (right next to the site), relative to being distant from it ($d \to \infty$).

This model is one of a family of 'excess relative risk' models that may be fit using the EPICURE computer package (Preston *et al.*, 1993). These take the form (slightly simplified):

$$R(\boldsymbol{z}_0, \boldsymbol{z}_1, \ldots, \boldsymbol{z}_J) = T_0(\boldsymbol{\beta}_0, \boldsymbol{z}_0)\Big[1 + \sum T_j(\boldsymbol{\beta}_j, \boldsymbol{z}_j)\Big],$$

where $\boldsymbol{z}_j$ and $\boldsymbol{\beta}_j$ represent vectors of covariates and parameters, respectively, and T_j represents a 'term' comprising in general the product of linear and loglinear 'subterms' $(\boldsymbol{\beta}^{\mathrm{T}}_{j(1)}\boldsymbol{z}_{j(1)}\exp(\boldsymbol{\beta}^{\mathrm{T}}_{j(2)}\boldsymbol{z}_{j(2)}))$. $R(\boldsymbol{z}_0, \boldsymbol{z}_1, \ldots, \boldsymbol{z}_J)$ may represent disease odds, odds ratio, hazard, or hazard ratio at given covariate values. Thus, for this application we have an entirely loglinear term $T_0(\exp(\boldsymbol{\beta}^{\mathrm{T}}\boldsymbol{x}))$ and a single other term T_1 with a linear subterm with a constant only (α), and a loglinear subterm in distance ($\exp(-\gamma d)$). Since this is a case–control study analysed as unmatched, $R(d, \boldsymbol{x})$ represents disease odds. EPICURE implements the maximum likelihood estimation and inference for this model for unmatched or matched (conditional likelihood) case–control data (as well as cohort and case–cohort data).

The development of the EPICURE family of models was motivated by the need to analyse studies of the effects of A-bomb survivors, in order to model the effects of radiation dose with respect to cancer, together with confounders and modifiers (Peirce and Preston, 1985; Pierce *et al.*, 1996). The model we have used also belongs to a family proposed independently specifically for use in case–control studies in the spatial context by Diggle and Rowlingson (1994).

$$\pi/(1-\pi) = \rho\exp(\beta^{\mathrm{T}}\boldsymbol{x})\{1 + g(d, \theta)\}$$

(slightly simplifying and changing notation to emphasise the similarities with our formulation). In our formulation, the parameter vector θ has two components α and γ, with $g(d, \theta) = \alpha\exp(-\gamma d)$. Diggle and Rowlingson's term ρ is subsumed in our formulation above as the constant term in $(\boldsymbol{\beta}^{\mathrm{T}}\boldsymbol{x})$, and their nearest specifically illustrated model uses d^2 where we have emphasised d, although we also fit a model using d^2.

Models allowing for effects that varied randomly between study areas (Smith *et al.*, 1995) were explored using the STATA, EGRET, and BUGS packages.

29.3 RESULTS

Fifteen study areas were defined around the 21 landfill sites. Table 29.1 shows the participating centres, study sites, study areas, study periods and numbers of cases and controls on which the current analyses are based. The total number of non-chromosomal cases and controls is 1089 and 2366, respectively. In Table 29.2 the relationship between two potential confounders, maternal age and socio-economic status, and the risk of congenital malformations is shown. Maternal age shows a slight gradient in risk with a higher odds ratio for older, compared with younger, mothers, but this trend is not statistically significant. There was no clear trend in the risk of congenital malformation in relation to socio economic status in any of the centres except in the United Kingdom, where the trend of increasing risk with increasing deprivation was statistically significant ($p = 0.04$). There appears not to be a consistent pattern of more deprived populations living closer to the waste sites (Figure 29.1).

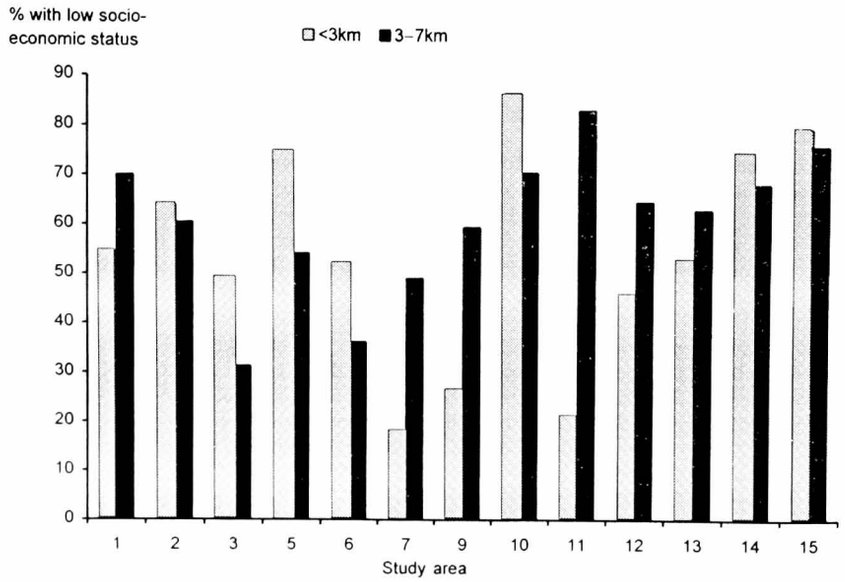

Figure 29.1 Percentage of controls with low socio-economic status close by and farther away from waste sites.
Notes: Areas 1, 2, and 5: % with social class 4 or 5 (from parental occupation);
Areas 6, 7: % in average area income quintiles 4 or 5 (lowest income areas);
Areas 9, 10, 11: % with less then high school eduction (maternal education);
Areas 3, 12–15: % in UK small-area deprivation quintiles 4 or 5 (most deprived areas);
Study area 4 and 8 have not been included in the graph because of small numbers

Table 29.3 Odds ratios for living within 3 km of a hazardous waste landfill site—non-chromosomal anomalies

	Distance	Cases	Controls	OR	95% CI	Adj. OR[a]	95% CI
All study areas pooled							
	0–3 km	295	511	1.37	1.14–1.63	1.33	1.11–1.59
	3–7 km	794	1855				
Study area							
1	0–3 km	7	23	0.49	0.15–1.63	0.43	0.11–1.65
	3–7 km	12	21				
2	0–3 km	11	25	1.26	0.47–3.40	1.23	0.41–3.67
	3–7 km	17	43				
3	0–3 km	25	59	1.16	0.60–2.26	0.76	0.34–1.69
	3–7 km	25	65				
4	0–3 km	6	18	1.12	0.19–6.42	0.83	0.11–6.07
	3–7 km	4	12				
5	0–3 km	4	14	0.58	0.17–1.91	0.45	0.13–1.60
	3–7 km	31	64				
6	0–3 km	18	21	2.19	1.08–4.45	2.08	0.98–4.41
	3–7 km	55	139				
7	0–3 km	11	11	2.92	1.11–7.70	3.93	1.20–12.80
	3–7 km	24	71				
8	0–3 km	0	1	0.00		–	
	3–7 km	6	15				
9	0–3 km	21	15	2.09	0.92–4.75	1.29	0.48–3.49
	3–7 km	39	52				
10	0–3 km	17	15	1.38	0.65–2.94	1.40	0.62–3.15
	3–7 km	104	123				
11	0–3 km	28	38	0.65	0.28–1.52	0.72	0.17–2.97
	3–7 km	17	15				
12	0–3 km	23	50	1.16	0.67–2.02	1.26	0.71–2.22
	3–7 km	97	250				
13	0–3 km	64	113	1.52	1.08–2.15	1.50	1.05–2.13
	3–7 km	232	627				
14	0–3 km	1	4	0.63	0.07–6.16	0.94	0.09–9.74
	3–7 km	22	54				
15	0–3 km	59	104	1.58	1.07–2.33	1.63	1.09–2.44
	3–7 km	109	304				

[a]Adjusted for socio-economic status and maternal age.
Note: The unadjusted odds ratios are not the cross-product ratios from the two-by-two tables because of the stratification by matching variables.

Table 29.3 presents the odds ratios for living within 3 km of a hazardous waste landfill site for each of the 15 study areas and for all study areas pooled, unadjusted and adjusted for maternal age and socio-economic status. The overall adjusted odds ratio was 1.33 (95% CI 1.11–1.59). Adjustment for confounders did not, either for the pooled

Table 29.4 Risk with distance from waste site—modelling of pooled data

Model					Deviance	d.f.	*p* (model)
Distance (D) categorised in 1 km bands							
D(km)	Cases	Controls	OR[a]	95% CI			
< = 1	41	62	1.60	1.03–2.48			
1–2	84	167	1.25	0.92–1.70			
2–3	170	282	1.46	1.15–1.85			
3–4	236	478	1.17	0.95–1.44			
4–5	206	469	1.06	0.86–1.32			
5–7	352	908	1.00				
					4199.8	5	0.025
Logistic regression model[a]							
$\pi/(1-\pi) = \exp(\beta \cdot distance)$			$\beta = -0.08$		4202.2	1	0.001
$\pi/(1-\pi) = \exp(\beta \cdot 1/distance)$			$\beta = 0.32$		4206.5	1	0.012
Exponential excess risk model[a]				95% CI			
1. $\{1 + \alpha \cdot \exp(-\gamma \cdot \text{distance})\}$			$\alpha = 1.18$ $\gamma = -0.28$	0.38–2.51[b]	4201.7	2	0.004
2. $\{1 + \alpha \cdot \exp(-\gamma \cdot \text{distance}^2)\}$			$\alpha = 0.55$ $\gamma = -0.03$	0.21–1.79[b]	4202.9	2	0.007
Null model[a]					4212.7	0	

[a] Adjusted for maternal age and socio-economic status.
[b] 95% CI estimated keeping γ fixed at its maximum likelihood value, and searching for values of α giving a deviance 3.84 greater than its value at the maximum likelihood estimate.

or individual study areas, substantially change the odds ratio estimates. Adjusted odds ratios for three study areas (7, 13 and 15) showed a statistically significant ($p < 0.05$) increase. The odds ratio for study area 6 borders significance. There was little evidence for heterogeneity in the odds ratios between sites ($p = 0.31$). Of several random effects approaches tried, only Bayes models giving high prior plausibility to large underlying variation suggested substantially different interpretations. A Bayes model with a normal distribution of underlying log odds ratios, and 'non-informative' gamma (0.001, 0.001) prior for the inverse variance of this normal distribution showed (crude) odds ratios distributed about a median of 1.35, with a 95% credible interval (1.07, 1.68).

Dividing subjects into six bands of distance (Table 29.4, Figure 29.2) showed a fairly consistent decrease in risk with distance. Several models using distance as a continuous variable fitted equally well, with the exponential excess model (shown in Figure 29.2) somewhat better than others (Table 29.4). All models showed a statistically significant decreasing risk with distance from the site ($p < 0.05$).

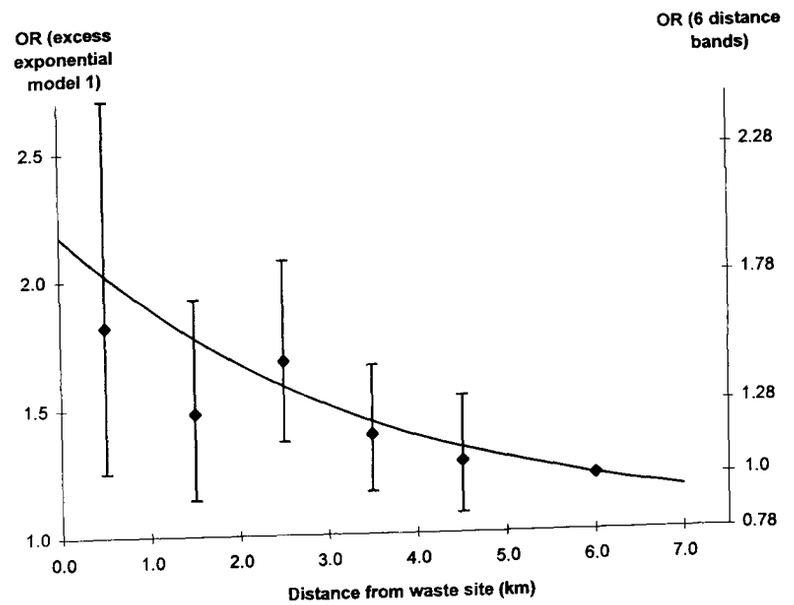

Figure 29.2 Risk with distance from waste site.
Notes: Line shows ORs fitted by exponential excess risk model; diamonds and error bars show ORs and 95% CI for 6 distance bands with 5–7 km band as baseline

29.4 DISCUSSION

Our study has shown a small but statistically significant excess risk of non-chromosomal congenital malformations among residents near (within 3 km of) landfill sites. This excess does not appear to be limited to one or a few sites, and indeed we have no evidence that the risk differs between sites, although our study has limited statistical power to address this issue. The fundamental question is, of course, whether this association is causal, but this cannot be resolved within this single study. Three questions are nevertheless relevant to the interpretation of this excess:

29.4.1 What do we know about potential confounders and sources of bias?

Socio-economic status is the most obvious potential confounder in any spatial analysis of health outcomes. More deprived communities may be both at greater risk of the adverse health outcome, and live closer to industrial sites. In the case of congenital malformations, there is surprisingly little literature to indicate the strength of the relationship

between socio-economic status and congenital malformation risk (Hemminki *et al.*, 1980; Knox and Lancashire, 1991; Olsen and Frische, 1993; Olshan *et al.*, 1991). Our own internal analysis has supported a positive association for non-chromosomal malformations with deprivation within the United Kingdom, but little indication of a relationship elsewhere. Although we found differences in the socio-economic profile between residents near and farther from individual sites, no overall pattern emerged for more deprived communities to be living near (within 3 km of) sites. Moreover, adjusting for socio-economic status in our statistical analyses resulted in very little shift in the odds ratios. We therefore conclude that socio-economic status is unlikely to explain the excess in congenital malformation risk found near sites.

A second source of confounding is the possible presence of other industrial sites or environmental exposures near landfill sites. We have not yet exhaustively examined this possibility, but it should be noted that to date there has been very little study of the risk of congenital malformation near any type of industrial site, and our results would have as much potential interest if they implicated other industrial sites as if they implicated the landfill sites under study.

Ascertainment bias, whereby higher case ascertainment occurred close to sites, is a theoretic possibility, but the participating registers had high case ascertainment through the use of multiple sources of information and active case finding, the data were routinely collected blind to the study hypothesis, and an examination of the data by hospital of birth shows that at least hospital-based ascertainment differences are not an explanation for the excess found near sites.

The migration of women between exposure and pregnancy outcome is a further potential source of bias, which would tend to lead to underestimation of any true raised relative risk. Among the chronic effects of exposure, congenital malformations and other adverse pregnancy outcomes are potentially some of the quickest to manifest in terms of the time that elapses between exposure and the detection of the adverse outcome (although for chemicals that bioaccumulate, the length of residence of the mother near the site may be important). Few estimates are available of the proportion of mothers who migrate during pregnancy, but recent figures from England suggest that about one quarter of women change address during pregnancy, of whom half move less than 1 km (Dolk, 1997). We estimate that this would lead to an approximately 10% underestimation of any true excess risk (Armstrong *et al.*, 1996).

29.4.2 To what extent can we distinguish differences in risk according to subgroups of malformations or landfill sites?

Congenital malformations are a very heterogenous set of conditions in terms of pathogenesis and aetiology, and it is thus of obvious interest to establish whether any particular malformations are preferentially linked to either landfill sites in general or to particular chemicals dumped in them. However, we are unable to derive from the literature any very strong a priori hypotheses about which anomalies should show a greater risk in general or in relation to specific chemicals. Furthermore, the landfill sites themselves cannot be classified into clearly differentiated groups according to the likely chemical exposures, both because each site tends to hold a range of chemicals, and because information on the chemicals dumped is incomplete, particularly going back in time when extensive record keeping was not a legal requirement. We established a number of

non-mutually exclusive congenital anomaly subgroups (i.e. one child could have more than one anomaly) according to what is known of the epidemiology of these conditions and current practice in surveillance, in order to 'explore' the data, rather than test any hypotheses. Inevitably, these subgroups were a compromise between lumping together heterogeneous conditions, and splitting into multiple subgroups with very few cases in each. Most subgroups exhibited raised odds ratios, with neural tube defects and malformations of cardiac septa and great arteries and veins having odds ratios of nominal statistical significance, and gastroschisis, hypospadias and tracheo-oesophageal fistulas of borderline significance. These results should be regarded as hypotheses to inform further study, but no great weight can be put on any interpretation of the differences in risk between congenital anomalies at this stage.

An analogous problem is distinguishing whether the overall excess risk within 3 km of landfill sites is a general attribute of all sites, or linked to particular sites. Formal testing of heterogeneity in odds ratios did not reveal any evidence of difference between sites, although the statistical power of such an analysis is low. Again, we believe that nothing can essentially be said about differences between individual sites. However, we are in the process of ranking sites according to their general 'hazard potential', using characteristics of their geology, engineering or management that would affect the likelihood of surrounding contamination. We believe that the demonstration of a 'dose-response' effect would strengthen the case for a causal association between the risk of congenital anomaly and residence near sites.

29.4.3 How would interpretation differ if we knew more about the background spatial distribution of the disease, and under what circumstances is more refined spatial modelling of use?

We have used spatial coordinates only to define the distance of cases and controls from the nearest waste site. Having done this, the statistical methods we have used have been standard epidemiological ones, rather than any specifically developed as 'spatial' (with the partial exception of the exponentially declining excess risk model). We believe that these methods have been largely adequate for this study. More explicitly spatial methods would allow one important refinement — allowing for a generalised spatial clustering of abnormalities. If such clustering exists, the finding of an excess near landfill sites is not as unusual as the nominal p-value would suggest. We could apply tests for such clustering and, by characterising it, perhaps in a spatial auto-correlation model, we could make a more appropriate inference on the importance of proximity to a site (Clayton and Bernardinelli, 1992). It may also be that spatial statistical methods would have a part to play in developing more refined indices of exposure.

The problems in interpretation here are not principally statistical, but related to the lack of evidence on exposure near the sites, and on plausible aetiological pathways.

29.4.4 European environmental surveillance

Finally, we would like to consider briefly the implications of this study for the environmental surveillance of congenital malformations at a European level. Environmental

problems are now not confined to any one country, and a coordinated policy response is necessary. If science is partly to underpin the policy process, this also needs to be coordinated at a European level. We have shown that it is possible to perform a multicentric study of congenital malformations in relation to a specific environmental point source in Europe. Although this sort of spatially oriented study is only one of many types of research angles needed, it responds to frequently expressed public concerns about spatial clusters, and is therefore valuable from a public health as well as a scientific point of view. Continuation and enlargement of this sort of enterprise requires: (a) more lines of communication being set up between environment departments and analysts of health data, such as congenital malformation registers; (b) a systematic system of control selection and geographical referencing being implemented (or routine post-coding of all births as in the United Kingdom); (c) more attention being given to the establishment of common or comparable European measures of socio-economic status so that socio-economic confounding can be properly included in studies; and (d) a source of funding that recognises the need for environmental surveillance to become part of the general surveillance process which is at present oriented much more towards the traditional concern of detection of clusters in time in relation to the introduction of new drugs.

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ACKNOWLEDGEMENTS

Study co-ordination was Funded by the European Commission DGXII BIOMED programme Concerted Action Contract BMH 1-94-1099.

APPENDIX 3 : Annexes 1-3 to the EC Directive on Hazardous Waste (12 December 1991, 91/689/EC)

ANNEX I

CATEGORIES OR GENERIC TYPES OF HAZARDOUS WASTE LISTED ACCORDING TO THEIR NATURE OR THE ACTIVITY WHICH GENERATED THEM (WASTE MAY BE LIQUID, SLUDGE OR SOLID IN FORM).

ANNEX 1.A.

Wastes displaying any of the propertes listed in Annex 3 and which consist of:

1. anatomical substances; hospital and other clinical waste;
2. pharmaceuticals, medicines and veterinary compounds;
3. wood perservatives;
4. biocides and phyto-pharmaceutical substances;
5. residue from substances employed as solvents;
6. halogenated organic substances not employed as solvents excluding inerty polymerized materials;
7. tempering salts containing cyanides;
8. mineral oils and oily substances (e.g. cutting sludges, etc.);
9. oil/water, hydrocarbon/water mixtures, emulsions;
10. substances containing PCBs and/or PCTs (e.g. dielectrics, etc.);
11. tarry materials arising from refining, distillation and any pyrolytic treatment (e.g. still bottoms, etc.);
12. inks, dyes, pigments, paints, lacquers, varnishes;
13. resins, latex, plasticizers, glues/adhesives;
14. chemical substances arising from research and development or teaching activities which are not identified and/or are new and whose effects on man and/or the environment are not known (e.g. laboratory residues)
15. pyrotechnics and other explosive materials;
16. photographic chemicals and processing materials;
17. any material contaminated with any congener of polychlorinated dibenzo-furan;
18. any material contaminated with any congener of polychlorinated dibenzo-p-dioxin.

ANNEX 1.B.

Wastes which contain any of the constituents listed in Annex 2 and having any of the properties listed in Annex 3 and consisting of:

19. animal or vegetable soaps, fats, waxes;
20. non-halogenated organic substances not employed as solvents;
21. inorganic substances without metals or metal compounds;
22. ashes and/or cinders;
23. soil, sand, clay including dredging spoils;
24. non cyanidic tempering salts;
25. metallic dust, powder;
26. spent catalyst materials;
27. liquids or sludges containing metals or metal compounds;
28. residue from pollution control operations (e.g. baghouse dusts, etc.) except (29), (30) and (33);
29. scrubber sludges;
30. sludges from water purification plants;
31. decarbonization residue;
32. ion-exchange column residue;
33. sewage sludges, untreated or unsuitable for use in agriculture;
34. residue from cleaning of tanks and/or equipment;
35. contaminated equipment;
36. contaminated containers (e.g. packaging, gas cylinders, etc.) whose contents include one or more of the contsituents listed in Annex 2;

37. batteries and other electrical cells;
38. vegetable oils;
39. materials resulting from selective waste collection from households and which exhibit any of the characteristics listed in Annex 3;
40. any other wastes which contain any of the constituents listed in Annex 2 and any of the properties listed in Annex 3.

ANNEX 2

CONSTITUENTS OF THE WASTES IN ANNEX 1.B. WHICH RENDER THEM HAZARDOUS WHEN THEY HAVE THE PROPERTIES DESCRIBED IN ANNEX 3 *).

Wastes having as constituents:

C1 beryllium; beryllium compounds;
C2 vanadium compounds;
C3 chromium (VI) compounds;
C4 cobalt compounds;
C5 nickel compounds;
C6 copper compounds;
C7 zinc compounds;
C8 arsenic; arsenic compounds;
C9 selenium; selenium compounds;
C10 silver compounds;
C11 cadmium; cadmium compounds;
C12 tin compounds;
C13 antimony; antimony compounds;
C14 tellurium; tellurium compounds;
C15 barium compounds; excluding barium sulfate;
C16 mercury; mercury compounds;
C17 thallium; thallium compounds;
C18 lead; lead compounds;
C19 inorganic sulphides;
C20 inorganic fluorine compounds, excluding calcium fluoride;
C21 inorganic cyanides;
C22 the following alkaline earth metals: lithium, sodium, potassium, calcium, magnesium, in uncombined form;
C23 acidic solutions or acids in solid form;
C24 basic solutions or bases in solid form;
C25 asbestos (dust and fibres);
C26 phosphorus: phosphorus compounds, excluding mineral phosphates;
C27 metal carbonyls;
C28 peroxides;
C29 chlorates;
C30 perchlorates;
C31 azides;
C32 PCBs and/or PCTs;
C33 pharmaceutical or veterinary compounds;
C34 biocides and phyto-pharmaceutical substances (e.g. pesticides, etc.);
C35 infectious substances;
C36 creosotes;
C37 isocyanates; thiocyanates;
C38 organic cyanides (e.g.nitriles, etc);
C39 phenols; phenol compounds;
C40 halogenated solvents;
C41 organic solvents, excluding halogenated solvents;

(*) Certain duplications of generic types of hazardous wastes listed in Annex 1 are intentional

C42 organohalogen compounds, excluding inert polymerized materials and other substances referred to in this Annex;
C43 aromatic compounds; polycyclic and heterocyclyc organic compounds;
C44 aliphatic amines;
C45 aromatic amines;
C46 ethers;
C47 substances of an explosive character, excluding those listed elsewhere in this Annex;
C48 sulphur organic compounds;
C49 any congener of polychlorinated dibenzo-furan;
C50 any congener of polychlorinated dibenzo-p-dioxin;
C51 hydrocarbons and their oxygen; nirtogen and/or sulphur compounds not otherwise taken into acount in this Annex.

ANNEX 3

PROPERTIES OF WASTES WHICH RENDER THEM HAZARDOUS.

H1 'Explosive': substances and preparations which may explode under the effect of flame or which are more sensitive to shocks or friction than dinitrobezene.
H2 'Oxidizing': substances and preparations which exhibit exothermic reactions when in contact with other substances, particularly flammable substances.
H3-A 'Highly flammable':
- liquid substances and preparations having a flash point below 21° C (including extremely flammable liquids), or
- substances and preparations which may become hot and finally catch fire in contact with air at ambient temperature without any application of energy, or
- solid substances and preparations which may readily catch fire after brief contact with a source of ignition and which continue to be consumed after removal of the source of ignition, or
- gaseous substances and preparations which are inflammable in air at normal pressure, or
- substances and preparations which, in contact with water or damp air, evolve highly flammable gases in dangerous quantities.

H3-B 'Flammable': liquid substances and preparations having a flash point equal to or greater than 21° C and less than or equal to 55° C.
H4 'Irritant': non-corrosive substances and preparations which, through immediate , prolonged or repeated contact with the skin or mucous membrane, can cause inflammation.
H5 ' Harmful': substances and preparations which, if they are inhaled or ingested or if they penetrate the skin, may involve limited health risks.
H6 'Toxic': substances and preparations (including very toxic substances and preparations) which, if they are inhaled or ingested or if they penetrate the skin, may involve serious, acute or chronic health risks and even death.
H7 'Carcinogenic': substances and preparations which, if they are inhaled or ingested or if they penetrate the skin, may induce cancer or increase its incidence.
H8 'Corrosive': substances and preparations which may destroy living tissue on contacts.
H9 'Infectious': substances containing viable micro-organisms or their toxins which are known or reliable believed to cause disease in man or other living organisms.
H10 'Teratogenic': substances and preparations which, if they are inhaled or ingested or if they penetrate the skin, may induce non-hereditary congenital malformations or increase their incidence.
H11 'Mutagenic': substances and preparations which, if they are inhaled or ingested or if they penetrate the skin, may induce hereditary genetic defects or increase their incidence.
H12 Substances and preparations which release toxic or very toxic gases in contact with water, air or an acid.
H13 Substances and preparations capable by any means, after disposal, of yielding another substance, e.g. a leachate, which possesses any of the characteristics listed above.
H14 'Ecotoxic': substances and preparations which present or may present immediate or delayed risks for one or more sectors of the environment.

APPENDIX 4 : Questionnaire for the Characterisation of Landfill Sites

QUESTIONNAIRE FOR CHARACTERISATION OF LANDFILL SITES

A. Site parameters

B. Geology and hydrology

C. Operational details

D. Types of waste

E. Water management and leachate control

Name and location of the landfill site:

_____

_____

_____

A. SITE PARAMETERS

1. Is the site operational or non-operational (closed)?

- ❑ operational
- ❑ non-operational

2. When did waste deposition begin (year)?

3. If the site is a non-operational/closed site, when did waste disposal operations stop (year)?

4. Total area of the site i.e. area licensed for waste deposition (ha):

5. Area which has already been filled and restored (ha):
(N.B. restored = treated and covered; some sites are filled cell by cell)

6. Operational area of the site i.e. the area where waste has been/is being deposited but is not restored (ha):

7. Volume of the waste in place (already deposited; m^3):

8. Weight of waste in place (already deposited; tonnes):

9. Site location (tick one or more):

- ❑ river estuary (river mouth)
- ❑ hill top
- ❑ river bank
- ❑ sea-shore
- ❑ marshland (area of very wet and muddy land)
- ❑ basin (natural depression in ground surface) / quarry (site where earth/rocks/minerals have been removed, e.g. mine)
- ❑ flat, inland area; none of the above
- ❑ other, specify: _____

10. Has there been significant above ground disposal, i.e. more than is necessary to encourage run-off from the site and allow for settlement?

- ❑ yes, above ground disposal
- ❑ no

11. Dominant land use adjacent to the landfill:
- ❑ rough grazing
- ❑ barren/derelict
- ❑ large intensively farmed fields
- ❑ forestry
- ❑ small agricultural holdings
- ❑ urban lands
- ❑ other e.g. amenity or recreation land

12. If the site is a non-operational (closed), or partially closed/restored site, what is the site area now used for?
- ❑ rough grazing
- ❑ barren/derelict
- ❑ large intensively farmed fields
- ❑ forestry
- ❑ small agricultural holdings
- ❑ urban lands
- ❑ other e.g. amenity or recreation land

13. Proximity of nearest building which forms part of residential area:
- ❑ < 50m
- ❑ 50-100m
- ❑ 100-500m
- ❑ 500-1000m
- ❑ >1km

14. List all industries within 2 km from the site and give approximate distance from the site. Specify the type of industry and approximate number of workers.

type of industry	distance from site	number of workers

B. GEOLOGY AND HYDROLOGY

15. Landfill base predominant rock type:
- ❑ clay
- ❑ sands
- ❑ gravels
- ❑ sandstones
- ❑ limestones
- ❑ chalk
- ❑ granite/hard rock
- ❑ other, specify: _____
- ❑ not known

16. Landfill sides predominant rock type
- ❑ clay
- ❑ sands
- ❑ gravels
- ❑ sandstones
- ❑ limestones
- ❑ chalk
- ❑ granite/hard rock
- ❑ other, specify: _____
- ❑ not known

17. Any lining of the landfill site:
- ❑ none
- ❑ all sides and base
- ❑ all sides
- ❑ all base
- ❑ partial sides
- ❑ partial base
- ❑ other, specify: _____

18. Is the treatment/lining:
- ❑ none
- ❑ a man-made liner
- ❑ bentonite (an impermeable clay) or clay liner
- ❑ liner made of in situ material
- ❑ granular / semi-permeable liner
- ❑ other, including combinations, specify: _____

19. What is the containment principle (i.e. is the site designed to stop wastes migrating, or is it designed to allow slow dispersal and dilution of waste)?
- ❑ containment
- ❑ dilute and disperse

please describe: _____

C. OPERATIONAL DETAILS

20. Are records kept of types of incoming waste?
- ❑ yes
- ❑ no

21. Are records kept of the weight of incoming waste?
- ❑ yes
- ❑ no

22. Are records kept of the volume of incoming waste?
- ❑ yes
- ❑ no

23. How many waste vehicles/containers deliver to the site on an average week day? _____

24. Is the newly added waste covered every day?

- ❑ yes
- ❑ no
- ❑ not known

25. What is the number of staff on-site? _____

D. TYPES OF WASTE

26. Annual input in tonnes:

	tonnes
- Inert waste - soil, building material, etc.	
- Commercial/industrial waste (non-hazardous)	
- Domestic waste - household	
- Hazardous solids	
- Hazardous liquids	

27. Does the waste site contain any of the following hazardous substances? (please tick which ones apply, and give the approximate annual input)

	approximate annual input tonnes):
❑ heavy metals	
❑ PCBs	
❑ organic solvents	
❑ pesticides	
❑ dioxins	
❑ others, please describe:	

E. WATER MANAGEMENT AND LEACHATE CONTROL

28. Is the quality of leachate within the waste site monitored?

- ❑ yes
- ❑ no

29. Is groundwater monitored in the vicinity of the landfill site?
- ❑ yes
- ❑ no

30. Is the surface water in the vicinity of the landfill site monitored?
- ❑ yes
- ❑ no

31. Is adjacent land monitored for the presence of landfill gas on a routine basis?
- ❑ yes
- ❑ no

32. Has monitoring shown (tick one or more):
- ❑ no pollution
- ❑ groundwater pollution
- ❑ surface water pollution
- ❑ migration of landfill gas
- ❑ not known

33. Were any measures incorporated into the landfill design to control leachate?
- ❑ no
- ❑ yes, specify: _____

34. Were any measures incorporated into the landfill design to control landfill gas?
- ❑ no
- ❑ yes, specify: _____

35. Have/will capping materials be used to reduce rainfall infiltration and prevent gas release?
- ❑ no 'cap' applied
- ❑ clay or similar natural material
- ❑ plastic/man-made membrane
- ❑ other, specify: _____

APPENDIX 5 : EUROHAZCON List of Congenital Anomalies for Inclusion

EUROHAZCON List of Congenital Anomalies for Inclusion

A case with one or more of these anomalies should be included. All associated anomalies of those cases should be described, whether or not they appear on the list for inclusion.

Syndromes consisting of one or more of the listed anomalies should be included.

Anomalies should be described in writing as well as coded according to the ICD 9, ICD 9 with BPA extension, EUROCAT 9, or ICD 10. Please indicate on the transmission form which coding system was used in each case. As much detail as possible about exact diagnostic description should be given.

EXCLUSIONS:

Cases with the following anomalies are not to be selected for the EUROHAZCON study unless occurring in combination with other specified anomalies on the inclusion list :

- EUROCAT list of minor anomalies for exclusion (see at end of this appendix);
- tumours and neoplasms;
- metabolic anomalies;
- deformations;
- cases showing 'familial' transmission are excluded only if parent carrier status is known.

INCLUSIONS:	**ICD 9 / BPA Code:**
Nervous system	
- anencephalus (incl. craniorachischisis)	7400-7401
- iniencephaly (please specify whether associated with anencephaly or spina bifida)	7402
- spina bifida	7410 and 7419
- encephalocele (include Meckel syndrome, specifying the syndrome clearly and the basis for diagnosis. Meckel syndrome may subsequently be excluded from some analyses)	7420
- microcephaly if head circumference more than 3 SD below the mean (please give head cicumference and age at measurement)	7421

- holoprosencephaly/arhinencephaly, including cyclops (please specify the extent of facial and brain anomalies and other features)	74266
- hydrocephaly, if congenital origin is verified.	7423
- other specified anomalies of brain, includes: anomalies of cerebrum or cerebellum, agyria and lissencephaly, microgyria, porencephaly and cerebral cysts	74220, 74223-74225 74241-74242
Eye	
- anophthalmos or microphthalmos (please specify whether unilateral or bilateral, and the degree of microphthalmia)	7430 and 7431
- corneal anomalies (absence, megalo, micro, opacity)	74322, 74340-74341
Ear	
- absence of auricle/ear	74401
- microtia	74421
Cardiac Anomalies	
Bulbus cordis anomalies and anomalies of cardiac septal closure:	
- common truncus	7450
- transposition of great vessels	7451
- tetralogy of Fallot	7452
- common ventricle	7453
- ventricular septal defect	7454
- ostium secundum type atrial septal defect (ASD included only if diagnosis is verified after 1 month of age, by echocardiography, postmortem, surgery, or catherisation)	7455
- endocardial cushion defects	7456
- cor biloculare	7457
- other	7458
- unspecified defect of septal closure	7459
Other anomalies of heart:	
- anomalies of pulmonary valve	7460
- tricuspid atresia and stenosis, congenital	7461
- Ebstein's anomaly	7462
- congenital stenosis of aorctic valve	7463
- congenital insufficiency of aoartic valve: includes aortic insufficiency, but excludes bicuspid aortic valves as only diagnosis.	7464
- congenital mitral stenosis	7465

- congenital mitral insufficiency	7466
- hypoplastic left heart syndrome	7467
- other specified anomalies of heart (excluding 74687: congenital heart block)	74680-74686 and 74688
Other congenital anomalies of circulatory system:	
- patent ductus arteriosus only for babies with gestational age of 37 weeks or more. (PDA included only if diagnosis is verified after 1 month of age, by echocardiography, postmortem, surgery, or catherisation)	7470
- coarctation of aorta	7471
- other anomalies of aorta	7472
- anomalies of pulmonary artery	7473
- total anomalous pulmonary venous return	74742
- partial anomalous pulmonary venous return	74743
Anomalies of respiratory system (excluding 74851: lung hypoplasia)	7480-7488 (excl 74851)
Facial clefts	
- cleft palate without cleft lip (if Pierre Robin, specify all components)	7490
- cleft lip without cleft palate	7491
- cleft lip and cleft palate	7492
Digestive system	
- tracheo-oesoph fistula, oesophageal atresia and stenosis	7503
- atresia and stenosis of small intestine	7511
- atresia and stenosis of large intestine, rectum and anal canal	7512
Other specified digestive system (excl pyloric stenosis):	
- other specified anomalies of oesophagus	7504
- other specified anomalies of stomach	7507
- other specified anomalies of alimentary tract	7508
- Hirschprung's disease and other congenital disorders of colon	7513
- anomalies of intestinal fixation	7514
- other anomalies of intestine	7515
- anomalies of gallbladder, bile ducts, and liver	7516
- anomalies of pancreas	7517
- other specified anomalies of digestive system:	7518

External genitals	
- anomalies of cervix, vagina, and external female genitalia	7524
- hypospadias (specify degree of hypospadias, excluded when the meatus lies before the coronary sulcus)	75260
- indeterminate sex (specify sex chromosomes)	7527
Urinary tract and kidney	
- renal agenesis/dysplasia/aplasia, unilateral and bilateral	75300-75301
Cystic kidney disease:	
- renal cyst (single)	75310
- polycystic kidneys, infantile type	75311
- polycystic kidneys, adult type	75312
- polycystic kidneys, NOS	75313
- medullary cystic disease	75314-75315
- multicystic kidney - unilateral	75316
Renal structural anomalies:	
- duplex kidney	75331
- horshoe kidney	75332
Renal drainage abnormalities:	
- atresia, stricture or stenosis of ureter leading to dilated kidney (obstruction confirmed by surgery before 1 year)	75321
- megaloureter / dilated ureter (always with dilated kidney)	75322
- dilated kidney (obstruction not proven)	75329
Dilated bladder:	
- congenital posterior urethral valves / urethral valves	75360
- obstruction, atresia or stenosis of anterior urethra / urethral atresia	75362
- with bilateral upper tract dilatation, usually severe / Prune belly syndrome	75672
Other anomalies of bladder:	
- extrophy of bladder	7535
- absence of bladder or urethra	75380
Limb reduction defects: (specify which limbs affected, and describe anomaly in detail)	7552-7554
Miscellaneous anomalies	
- branchial cleft anomalies	7444
- anomalies of vertebrae	75614-75618
- absence of ribs	75630

- chondrodystrophy and skeletal dysplasia	7564
- osteodystrophies	7565
- absence of diaphragm	75660
- diaphragmatic hernia	75661
- exomphalos/omphalocele (exclude umbilical hernia)	75670
- gastroschisis	75671
- ichthyosis congenita (specify genetic origin if appropriate)	7571
- other well specified anomalies of skin (excluding skin tags, naevus, and birthmark with surface less than 4 cm^2)	7573 (excl. 75731 and 75738)
- well specified anomalies of hair and nails	7574-7575
- well specified anomalies of integument	7578
Chromosomal anomalies (excluding unspecified anomalies and balanced translocations where one parent is identified as carrier; specify karyotype)	7580-7588
Conjoined twins	7594
Syndromes, with or without other anomalies for inclusion (for genetic syndromes note that diagnosed 'familial' cases with known parent carrier status are excluded)	

EUROCAT list of 'minor anomalies' for exclusion

Cases with the following anomalies are not to be selected for the EUROHAZCON study unless occuring in combination with other specified anomalies on the inclusion list:

Anomalies of eye:
- Stenosis or stricture of lacrimal duct (74365)
- Congenital ptosis (74360)

Anomalies of ear:
- Minor or unspecified anomaly of ear (7442)
- Preauricular appendage, tag or lobule (74411)
- Other appendage, tag or lobule (74412)
- Macrotia (7442)
- Bat ear (74422)
- Misplaced ear (74424)

Cardiovascular system:
- Functional or unspecified cardiac murmur (7852)
- Absence or hypoplasia of umbilical artery, single unbilical artery (7475)
- Patent ductus arteriosus in premature (< 37 weeks) babies (7470)

Digestive system:
- Tongue tie (7500)
- Meckel's diverticulum (75101)
- Pharyngeal pounch (75020)

External genitalis:
- Undescended testicle (7525) and unspecified ectopic testis (75253)
- Congenital hydrocele or hydrocele of testis (7786)
- Phymosis (605)
- Hypospadia when the meatus lies before the coronary sulcus, glandular or 1st degree hypospadias (75260)

Limbs:
- Clicking hip (75432)
- Clubfoot of postural origin (75473)
- Postural or unspecified metatarsus varsus or metatarsus adductus (75452)
- Postural or unspecified talipes calcaneovalgus or pes calcaneovalgus (75460)
- Minor or unspecified anomalies of toe such as hallux valgus, hallux varus, or "orteil en marteau" (75560)

Other musculoskeletal anomalies and anomalies of the integument:
- Spina bifida occulta uncomplicated (75610)
- Pectus excavatum (75636 or 75481)
- Minor or unspecified anomaly of nose (74819)
- Minor or unspecified deformity of face (74491)
- Minor anomaly of nipple (75768)
- Accessory or ectopic nipple (75765)
- Congenital umbilical hernia (5531), inguinal hernia (550), para umbilical (5531), ventral or incisional (5532), hiatus hernia (7506)
- Abnormal palmar crease (7572)
- Skin tag with surface less than 4 cm^2 : skin tag (75731), naevus (75738), angioma (2280), haemangioma (2280), glomus tumor (2280), lymphangioma (2281), birthmark (75738)
- Sacral dimple (7578 or 6851)
- high arched palate (75024)

APPENDIX 6 : Data Transmission Form and Instructions for Coding

PAGE

NUMBERING

AS ORIGINAL

DATA TRANSMISSION FORM - EUROHAZCON

SECTION A: TO BE COMPLETED FOR CASES AND CONTROLS

Centre: _____

Local id No. of this case/control: _____

Case or control: case ❑ 1
control ❑ 2

1. If *control*, please give the local id **no**. of the case for which this is the control:

local id no. of case: _____

Is a twin or sib of this case/control also in the dataset? yes ❑ 1
no ❑ 2
not known ❑ 9

1. If *yes*, give the local id no(s). of the twin/sib(s): _____

5. Geographic co-ordinates of residence **at** birth (if U.K. centre give full postcode):

5a. X co-ordinate (or postcode if in U.K.): _____

5b. Y co-ordinate: _____

6. Site code of nearest landfill site: _____

7. Distance from nearest landfill site: _____ metres

If this case/control is within 7 km of other landfill site(s) give the site code of these other landfill sites and the distance of residence from these sites:

Site Code:	Distance:
7a. _____	**7b.** _____ metres
7c. _____	**7d.** _____ metres

8. Date of birth (day/month/year): _____ / _____ / _____

9. Place of birth: hospital, local code: _____ 88
at home ❑
not known ❑ 99

10. Sex: male ❑ 1
female ❑ 2
indeterminate ❑ 3
not known ❑ 9

11. Number of babies delivered: singleton ❑
twins ❑
multiple, give no.: _____
not known ❑

12. Type of birth: live birth ❑
stillbirth ❑
spontaneous abortion ❑
induced abortion ❑
not known ❑

13. Birth weight: _____ grams

14. Length of gestation: _____ weeks

15. Socio-economic status (local code): _____

MOTHER

16. Age of mother at delivery: _____ years

Reproductive history:

17. Number of previous spontaneous abortions: known, give no.: _____
not known ❑

18. Number of previous induced abortions: known, give no.: _____
not known ❑

19. Number of previous stillbirths: known, give no.: _____
not known ❑

20. Number of previous live births: known, give no.: _____
not known ❑

21. Number of total previous pregnancies: known, give no.: _____
not known ❑

SECTION B: TO BE COMPLETED FOR CASES ONLY

22. Age of father at delivery: _____ years

23. Did the case survive beyond one week (7 days) of age? yes ❑
no ❑
not known ❑

4. Has a chromosomal analysis (karyotyping) been done? done, result known ❑ 1
done, result not known ❑ 2
not done ❑ 3
failed ❑ 8
not known ❑ 9

If done, please give karyotype: _____

5. Has a post mortem examination been carried out? done, result known ❑ 1
done, result not known ❑ 2
not done ❑ 3
macerated fetus ❑ 4
not known ❑ 9

MALFORMATIONS:

6. Syndrome:

_____ ☐☐☐☐☐☐

7. Malformations present:

27.1: _____ ☐☐☐☐☐☐

27.2: _____ ☐☐☐☐☐☐

27.3: _____ ☐☐☐☐☐☐

27.4: _____ ☐☐☐☐☐☐

27.5: _____ ☐☐☐☐☐☐

27.6: _____ ☐☐☐☐☐☐

27.7: _____ ☐☐☐☐☐☐

27.8: _____ ☐☐☐☐☐☐

additional malformations:

28. Which coding system was used to code the malformations (question 26 and 27) of this case?
ICD 9 ❑ 1
ICD 9 with BPA extension ❑ 2
EUROCAT version based on ICD9 ❑ 3
ICD 10 ❑ 4
other, please specify: _____ 5
not known ❑ 9

PDA/ASD cases only:

29. If this case has a patent ductus arteriosus (PDA) or an atrial septum defect (ASD), was th diagnosis verified after 1 month of age by echocardiography, postmortem, surgery, or catherisation?
yes ❑
no ❑
not known ❑

30. Does the child have a recognisable *monogenic* syndrome?
yes ❑
no ❑
not known ❑

30a. If yes, what is the type of Mendelian inheritance of this syndrome?
autosomal dominant ❑
autosomal recessive ❑
X-linked ❑
not known ❑

30b. If known, give the McKusick code of this syndrome: _____

31. Is there parental consanguinity?
yes ❑
no ❑
not known ❑

If yes, what relationship are the parents to each other? _____

_____

32. Are any of the child's siblings affected with the same or other malformations?
yes ❑
no ❑
not known ❑

If yes, please specify anomalies for each affected sibling: _____

_____

_____

33. Are any members of the mother's or father's family (including the mother and the father) affected with the same or other anomalies?
yes ❑
no ❑
not known ❑

If yes, please give details (relation to the child, type of malformations):

_____

_____

no.	Variable	Digits	Code	Instructions
			SECTION A : TO BE COMPLETED FOR CASES AND CONTROLS	
1	Centre	2	01 = Northern Region 02 = Odense 03 = North West Thames 04 = North East Italy 05 = Tuscany 06 = Glasgow 07 = Antwerp 08 = Slovenia 09 = Lyon 10 = England and Wales Down Syndrome Register	- Enter allocated code, or specify name of registry in writing.
2	Local identification no.	11	local code	- Each case and each control should have a unique identification number. - The number is a maximum of 11 characters long. - For twins where both malformed, give different local code for each.
3	Case or control	1	1 = case 2 = control	- Enter whether this infant is a case or a control birth.
If control:				
3a	Local identification no. of case	11	local code	- If the infant is a control, please enter the identification number of the case for which this is the control. - Leave blank if infant is case.
4	Twin or sib(s) in dataset	1	1 = yes 2 = no 9 = not known	- Enter whether this infant has a twin or sib(s) in this dataset.
If twin or sib in dataset:				
4a	Local identification no. of twin/sib	11	local code	- If a twin or sib(s) in this dataset, please enter the identification number of this twin/sib. - If more than one twin/sib in the dataset, create variable 4b, 4c etc. for local identification number of these twins/sibs. - Leave blank if no sibs/twins in dataset.
5	Geographic co-ordinates of residence at birth			- Geographic co-ordinates of the address of the mother at the time of birth of the infant. - Give geographic co-ordinates/grid reference as used in your country, with an accuracy of at least 100m. - For U.K. centres give postcode of residence of the mother at the time of birth
5a	X co-ordinate	8	local grid reference	- X co-ordinate (easting) of local grid reference, or U.K. postcode.
5b	Y co-ordinate	8	local grid reference	- Y co-ordinate (northing) of local grid reference.

no.	Variable	Digits	Code	Instructions
6	Site code of nearest landfill site	2	local site identification code	- Each landfill site included in this study should have a local identification code. - The site identification code is 2 digits long.
7	Distance from nearest landfill site	4	metres: 0-7000	- Distance from nearest landfill site included in this study to residence at birth in metres.
If within 7 km of other landfill site (other than the nearest landfill site):				
7a	Site code of other site A	2	local site identification code	- If this case/control is within 7 km of another landfill site included in this study, give the site code of this other site under question 7a and give the distance of residence from this site under question 7b. - If this case/control is within 7 km of two other sites, fill in question 7c and 7d as well. - If this case/control is not within 7 km of any other waste site included in the study than the nearest site, leave questions 7a-7d blank.
7b	Distance to other site A	4	metres: 0-7000	- Distance of residence from other landfill site in metres
7c	Site code of other site B	2	local site identification code	- see instructions for question 7a.
7d	Distance to other site B	4	metres: 0-7000	- Distance of residence from other landfill site in metres.
8	Date of birth	6	day/month/year	- The date of birth/abortion should be known for all cases and controls - e.g. 21 July 1988 code 210788
9	Place of birth	2	local code of hospital/institution 88 = home 99 = not known	- Use local code (2 digits) to identify hospital or other institution of birth. - Each hospital / institution should have a separate code
10	Sex	1	1 = male 2 = female 3 = indeterminate 9 = not known	- Indicate chromosomal sex, if known, in case of ambiguous genitalia. - Indicate indeterminate sex in case of ambiguous genitalia with unknown or abnormal sex chromosome complement. - If sex could not be determined at autopsy due to maceration or other problems, indicate as "not known".
11	Number of babies delivered	1	1 = singleton 2 = twins 3 = triplets, etc. 9 = not known	- Cases: complete one form for each malformed baby in a multiple delivery (not for other, normal, babies in the multiple set). - Controls: if a control birth is from a multiple delivery, only complete the form for the selected control (not for other babies in the multiple set). - Only one form is to be completed for conjoined twins.
12	Type of birth	1	1 = live birth 2 = stillbirth 3 = spontaneous abortion 4 = induced abortion 9 = not known	- The distinction between live birth, stillbirth and spontaneous abortion should follow the definitions in use in your country. - Stillbirths, spontaneous abortions, and intra-uterine deaths with a gestational age of less than 20 weeks are excluded. - Make sure that both birth weight and gestational age are recorded.

no.	Variable	Digits	Code	Instructions
13	Birth weight	4	grams 9999 = not known	- Birth weight in grams.
14	Length of gestation	2	weeks 99 = not known	- In completed weeks after first day of last menstrual period (LMP).
15	Socio-economic status	1	local coding 9= not known	- Use local coding system to classify socio-economic status. Variables such as occupation of mother and/or father, education of mother and/or father, can be used for the classification of socio-economic status. - Do not use more than 8 different classes. - Provide a detailed explanation of the local coding. - Code BLIND to case/control status.
16	Age of mother at delivery	2	years 99 = not known	- In completed years at the time of delivery. - Use expected date of delivery for terminations of pregnancy.
	Reproductive history:			
17	Number of previous spontaneous abortions	1	0 = none 1= one 2 = two etc. 9 = not known	- If a twin pregnancy aborted count as 2.
18	Number of previous induced abortions	1	0 = none 1= one 2 = two etc. 9 = not known	- At any gestational age, whether for medical or other reasons. - If a twin pregnancy aborted count as 2.
19	Number of previous stillbirths	1	0 = none 1= one 2 = two etc. 9 = not known	- A twin delivery counts as 2, if both stillborn.
20	Number of previous live births	2	00 = none 01= one 02 = two etc. 99 = not known	- A twin delivery counts as 2, if both live born.
21	Total number of previous pregnancies	2	00 = none 01= one	- This is total number of previous pregnancies, not births. - The present notified pregnancy is not to be included.

no.	Variable	Digits	Code	Instructions
			02 = two etc. 99 = not known	- All previous abortions, whether spontaneous or induced, are included. - Previous twin or multiple pregnancies count as one in total.

SECTION B : TO BE COMPLETED FOR CASES ONLY :

22	Age of father at delivery	2	years 99 = not known	- In completed years at the time of delivery.
23	Survival beyond one week of age	1	1 = yes 2 = no 9 = not known	- Yes = child known to be alive at 7 days of age. - No = child known to be dead at or before 7 days of age (include stillbirths, abortions, and neonatal deaths).
24	Chromosomal analysis (karyotyping)	1	1 = done, result known 2 = done, result not known 3 = not done 8 = failed 9 = not known	- If karyotyping is done and the result known, please specify karyotype in writing. - "Failed" refers to a technical failure where repeat examination could not be done and the karyotype is therefore unknown.
25	Post mortem examination	1	1 = done, result known 2 = done, result not known 3 = not done 4 = macerated fetus 9 = not known	- If post-mortem examination is done, record the malformation(s) discovered in the "malformations" section of the form. - "Result known" means that the autopsy record has been reviewed by the registry. - "Result not known" means that the autopsy record was not available to the registry. - "Macerated fetus" means that although a post mortem was performed, maceration of the fetus prevented a full protocol from being followed.
	MALFORMATIONS			
26	Syndrome	6	ICD code + written description	- Name of recognisable syndrome, association, eponym, or disease name. - Written description: write name of syndrome, association, etc., in full. - Start code in the most left hand box. - If fifth and/or sixth digit are not known or non-existent, leave blank. - If not a recognisable syndrome, association, eponym, or disease name, leave blank - When two syndromes are present in the same subject, code the most important one in the boxes for syndrome and the other in the boxes for the first malformation. - If a recognisable syndrome, eponym, or disease name, with no specific code, then code 8888 8 8 and specify name in writing.

no.	Variable	Digits	Code	Instructions
27.1	Malformation 1	6	ICD code + written description	- Written description: give in writing the fullest description of the malformation available.
27.2	Malformation 2	6		- Start the code in the most left hand box.
				- If the fifth and/or sixth digit are not known or non-existent, leave blank.
27.3	Malformation 3	6		- Up to 8 malformations can be coded. If more malformations are present, specify these in the space for additional malformations. Include in the eight coded
27.4	Malformation 4	6		malformations the most important ones.
				- Code under question 27 which coding system (ICD 9, BPA, ICD 10, etc.) was
27.5	Malformation 5	6		used to code this particular case.
				- Cases with no malformations on the list of inclusions (annex III) should be
27.6	Malformation 6	6		excluded.
				- When malformations from the inclusion list are present, all anomalies should be
27.7	Malformation 7	6		coded, whether on the inclusion list or not.
27.8	Malformation 8	6		
28	Coding system	1	1 = ICD 9 2 = ICD 9 with BPA extension 3 = EUROCAT version based on ICD 9 4 = ICD 10 5 = other, specify 9 = not known	- Enter which coding system was used to code the syndrome and malformations in questions 26 and 27.
For PDA and ASD cases only:				
29	Verification of diagnosis	1	1 = yes 2 = no 9 = not known	- Yes = The diagnosis of patent ductus arteriosus (PDA) or atrial septum defect (ASD) in this case was verified after 1 month of age, by echocardiography, post mortem, surgery, or catheterisation. - No = PDA or ASD was not verified, or only verified before 1 month of age, or only verified by other techniques, such as X-ray or ECG (not by echo, postmortem, surgery, or catheterisation). - If this case is not a PDA or ASD case, leave blank.
30	Monogenic syndrome / condition	1	1= yes 2 = no 9 = not known	- Record whether the child has a diagnosed, recognisable monogenic syndrome or condition. - A monogenic syndrome/condition is a condition with a single gene origin (autosomal recessive, autosomal dominant, or X-linked).
30a	Mendelian inheritance	1	1 = autosomal dominant 2 = autosomal recessive	- If the child has a diagnosed, recognisable monogenic syndrome/condition, record what the type of inheritance of this syndrome/condition is.

no.	Variable	Digits	Code	Instructions
			3 = X-linked 9 = not known	- Leave blank if not a monogenic syndrome/condition.
30b	McKusick code	5	99999 = not known	- If known, fill in the McKusick code of the syndrome/condition. - The full 5-digit code is to be found in McKusick's "Mendelian Inheritance in Man". - Leave blank if not a monogenic syndrome/condition.
31	Consanguinity	1	1 = yes 2 = no 9 = not known	- Yes = parents are related. Specify in writing what relationship the parents are to each other. - No = parents of this child are not related.
32	Anomalies of siblings	1	1 = yes 2 = no 9 = not known	- Code whether any of the child's siblings are affected with the same or other anomalies. - Specify in writing the type of anomaly for each sib.
33	Anomalies in family	1	1 = yes 2 = no 9 = not known	- Code whether any members of the mother's or father's family (including the mother and the father) are affected with the same or other anomalies. - Specify in writing the relation to the child and the type of malformations for each affected member of the family.

no.	*Group name*	*Malformations included*	*ICD9/BPA codes*
1	neural tube defects	anencephalus, spina bifida, encephalocele	740, 741, 7420
2	hydrocephaly	congenital hydrocephalus (without neural tube defect)	7423
3	microcephaly	microcephalus	7421
4	other specified brain anomalies	anomalies of cerebrum or cerebellum, agyria, lissencephaly, microgyria, holoprosencephaly, porencephaly, cerebral cysts	74220, 74223-74226, 74241-74242
04a	holoprosencephaly	holoprosencephaly	74226
5	eye anomalies	anophthalmos, microphthalmos, enlarged cornea, corneal opacity, other corneal anomalies	7430-31, 74322, 74340-1
05a	anoph/microphtalimia	anophthalmos, microphthalmos	7430, 7431
6	ear anomalies	absence of auricle/ear, microtia	74401, 74421
7	malformations of cardiac chambers and connections	common arterial trunk, double outlet right ventricle and left ventricle, discordonant ventriculoarterial and atrioventricular connection, double inlet ventricle, isomerism of atrial appendages, other and unspecified malfmations of cardiac chambers and connections	74500, 7451, 7453
8	malformations of cardiac septa	VSD, ASD, atrioventricular septal defect, Tetralogy of Fallot, artopulmonary septal defect, other and unspecified septal defects.	74501, 7452, 7454, 7455, 7456-7459
9	malformations of valves and other heart malformations	anomalies of pulmonary valves, tricuspid atresia and stenosis, Ebstein's anomaly, stenosis and insufficiency of aortic valve, mitral stenosis and insufficiency, hypoplastic left heart syndr., hypoplastic right heart syndr., other malformations of pulmonary, tricuspid, aortic and mitral valves. other specified heart anomalies.	7460-7467, 74680-74686 and 74688
10 (10a)	anomalies of great arteries and veins (with and without PDA)	patent dustus arteriosus (>=37 weeks), coarctation of aorta, other anomalies of aorta, anomalies of pulmonary artery, total and partial pulmonary venous return.	7470, 7471, 7472, 7473, 74742, 74743
11	anomalies of respiratory system	web of larynx, other larynx, trachea, and bronchus anomalies, cystic lung, agenesis and dysplasia of lung, other lung anomalies, other respiratory system anomalies	7482-7488 (excl. 74851)
12	nose anomalies	choanal atresia, other anomalies of nose	7480, 7481
13	cleft palate and cleft lip	cleft palate, cleft lip, cleft palate with cleft lip	7490-7492
13a	cleft palate	cleft palate	7490
13b	cleft lip with or without cleft palate	cleft lip, cleft lip and palate	7491 and 7492
14	tracheo-oesophageal anomalies	tracheo-oesophageal fistula, oesophageal atresia and stenosis	7503
15	digestive system and upper alimentary tract	other specified anomalies of oesophagus, stomach, alimentary tract, small intestine, large intestine, Hirschprung's, intestinal fixation, other intestine, gallbladder, liver, bile ducts, pancreas, other specified	7504, 7507, 7508, 7511, 75120, 7513-7518
16	atresia and stenosis of rectum and anal canal	stenosis, atresia, or absence of rectum or anus.	75121-75124

contd.

no.	*Group name*	*Malformations included*	*ICD9/BPA codes*
17	external genitalia (male)	hypospadias	75260
18	external genitalia (female + indeterminate)	anomalies of cervix, vagina, external female genitalia, indeterminate sex	7524, 7527
19	renal anomalies	renal agenesis and dysgenesis, cystic kidney disease, duplex kidney, horseshoe kidney, other specified	7530, 7531, 75331, 75332, 75338
20	urinary tract anomalies	obstructive defects of renal pelvis and ureter, exstrophy of urinary bladder, posterior urethral valves, obstruction, atresia, stenosis of anterior urethra, absence of bladder or urethra, vesico-urethral reflux, Prune Belly	7532, 7535, 75360, 75362 , 75380, 5937, 75672
21	limb reduction defects	upper, lower, and unspecified limb	7552, 7553, 7554
22	branchial cleft anomalies	branchial cleft, cyst, or fistula; preauricular sinus; Goldenhar's syndrome	7444; 75603; 75606
23	other musculoskeletal anomalies	anomalies of vertebrae, absence of ribs	75614-75618, 75630
24	chondodystrphy and osteodystrophy	chondrodystrophies, osteodystrophies	7564, 7565
25	anomalies of diaphragm	absence of diaphragm, diaphragmatic hernia, eventration of diaphragm	75660, 75661, 75662
26	anomalies of abdominal wall	exomphalos, gastroschisis	75670, 75671
26a	exomphalos	exomphalos	75670
26b	gastroschisis	gastroschisis	75671
27	skin and integument anomalies	well specified skin anomalies; ichthyosis congenita, well specified anomalies of hair, nails, other well specified integument anomalies	75730-75738, 2280, 7571, 7574-5, 7578
28	syndromes - presumed 'de-novo' mutations	non-chromosomal syndromes: presumed de novo, excl. familial transmission (individual malformations not coded under their respective sub-groups)	
29	multiple malformations	non-syndromic associations of 2 or more malformations for inclusion (2 or more of the main groups), where not a sequence (individual malformations also coded under their respective sub-groups); multiple cardiac, CNS, and renal urinary malformations not regarded as multiple anomalies.	
30	miscellaneous sequences	Poland, Ivemmark, Robin (not classified under respective subgroups)	
31	chromosomal anomalies	chromosomal anomalies (individual malformations not coded under their respective sub-groups)	7580-7588,75890-75898
31a	Downs syndrome	Down syndrome (individual malformations not coded under their respective sub-groups)	7580
31b	Non-Down Syndrome chromosomal anomalies	Patau's Syndrome, Edward's Syndrome, Autosomal deletion syndromes, other conditions due to autosomal anaomlies, Turner's syndrome, Kliefelter's syndrome, other conditions due to sex chromosome anomalies, other specified chromosmal anomalies	7581-7588,75890-75898

APPENDIX 8 : Adaptation of Existing Hazard Scoring System and Comparison with Expert Panel Hazard Scoring

This appendix describes, in part A, the adaptation of an existing site ranking system (JRB Associates, 1982, see also section 2.1) to classify EUROHAZCON study sites according to their hazard potential. This methodology was not used for final classification of the EUROHAZCON study sites. Part B of this appendix describes the comparison of the adapted JRB system with the expert panel scoring described in section 3.6 of this thesis.

Part A. Adaptation of an Existing Hazard Scoring System

The site rating methodology developed by JRB Associates (1983) seemed attractive for use in this study because it did not require site visits or extensive site investigations. The original JRB ranking system consists of 'rating factors' in 4 categories (Table 1) which are each scored using a 4 level 'rating scale' (0 to 3), and a weighting factor, the so-called 'multiplier'.

In consultation with some of the local landfill specialists collaborating with EUROHAZCON [PP, GB, BD] substantial adaptations were made to the JRB system, excluding or changing factors that were considered not relevant or for which it was not thought to be feasible to obtain information. The following main adaptations were made:

- The JRB system was originally developed to identify sites for clean-up priority and therefore includes some factors that do not need to be part of the site ranking in this study, for example size of nearby population (already reflected in numbers of cases and controls) and distance to nearest building. Such factors have been excluded in the adaptation.
- For the EUROHAZCON study we were only interested in the toxic (and in particular teratogenic) properties of waste (i.e. not its flammability, corrosiveness, etc.). It was agreed between participants that it would not be feasible to systematically rank chemicals by their teratogenicity. Moreover, without detailed information on the type and quantity of each chemical present, the tendency to have a general mix of different chemicals makes use of toxicity as an element in the ranking system seem impossible. Factors concerning waste characteristics have therefore been excluded from the adaptation.
- In order to distinguish between the two main pathways of exposure (water and air) it was decided to divide factors relating to receptors, pathways and management practices into

those that are most relevant for exposure through water, those that are most relevant in determining air exposure, and those that play a role in both (general).

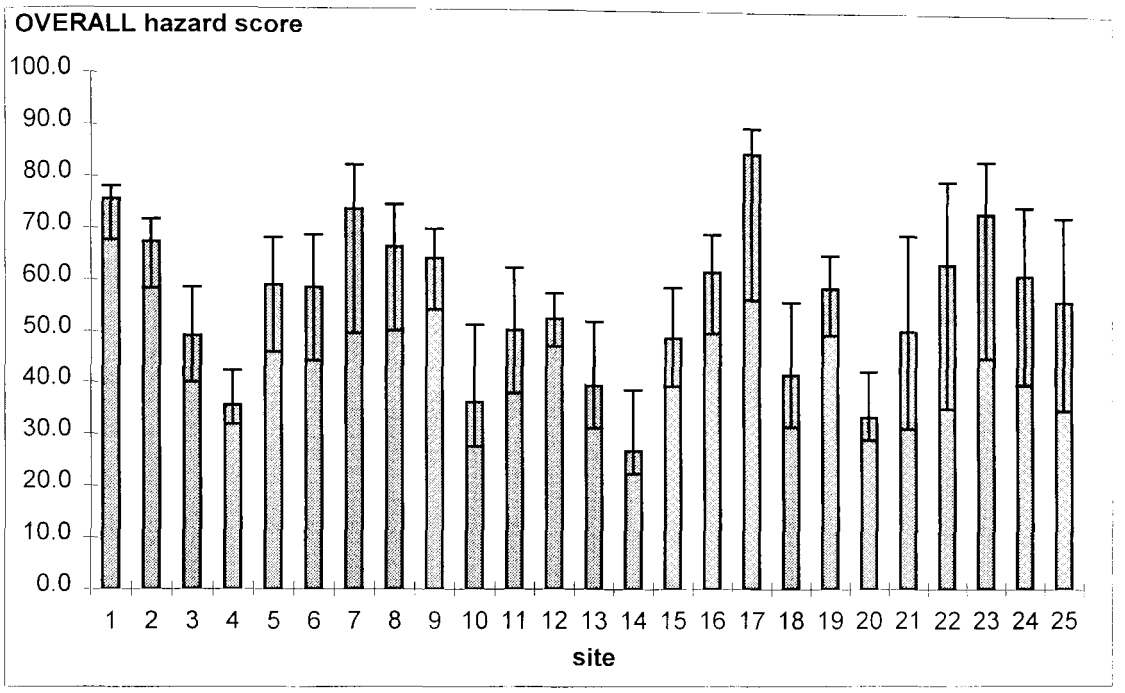
Factors included in the original JRB and in the adapted scoring system are shown in Table 1. The final ranking categories are *water*, which combines the water pathway and general site characteristics, *air,* which combines the air pathway and general characteristics, and *overall,* which combines all three sub-categories. Multipliers and rating scale levels applied to the ranking factors in the adapted system were kept as close as possible to original JRB system but were changed where needed to reflect the range of possible answers from the Landfill Site Ranking Questionnaire. The multipliers and rating scales in the adapted system are shown in Part C of this appendix.

Table 1: Ranking factors included in the original JRB Associates Site Rating Methodology and the system adapted for EUROHAZCON

JRB system factors	*Adapated system factors*
RECEPTORS	WATER PATHWAY
population within 1,000 feet	distance to nearest drinking water supply
distance to nearest drinking water well	distance to nearest surface water
distance to nearest off-site building	depth to groundwater
land use	annual precipitation
critical environment	soil permeabilty
	evidence of contamination
PATHWAYS	level of contamination
evidence of contamination	type of contamination
level of contamination	monitoring
type of contamination	use of liners
distance to nearest surface water	type of liners
depth to groundwater	use of leachate collection system
net precipitation	
soil permeability	AIR PATHWAY
bedrock permeability	evidence of contamination
depth to bedrock	lvel of contamination
	type of contamination
WASTE CHARACTERISTICS	monitoring
radioactivity	use of gas collection system
persistence	daily cover
ignitability	capping
corrosiveness	
solubility	GENERAL
volatility	land use within 3 km of the site
physical state	years since start of site operation
	history of site management
WASTE MANAGEMENT PRACTICES	hazardous waste quantity
hazardous waste quanity	total waste quantity
total waste quanity	
waste incompatibility	
use of liners	Final Ranking categories:
use of leachate collection system	water = water pathway + general
use of gas collection system	air = air pathway + general
use and condition of containers	overall = water pathway + air pathway + general
cover and capping	

Overall hazard potential scores calculated using the adapted system are shown in Figure 1 for the 25 study sites for which questionnaire information was available. For each score a range was calculated giving the minimum and maximum possible scores based on minimum and maximum values for missing factors; a wider range reflects missing information for a larger number of factors.

Figure 1 : Overall hazard scores and range calculated from adapted ranking system



In order to assess how sensitive the adapted system was to changes in the factors and multipliers some sensitivity analyses were carried out showing, in summary :

1. If ranking factors are taken out one by one, the number of sites that change score quintile in the overall scoring is generally small: 20 out of 24 factors included in the overall scoring led to a change in score quintile of between 0 and 4 sites when taken out. The other 4 factors when taken out led to changes in score quintiles for 6 sites. More changes are seen for air and water: 12 out of 17 factors included in the water score and 8 out of 12 factors included in the air score led to a change in score quintile in 6 or more sites when taken out. Taking out the factor 'total waste quantity' had the largest effect: 11 sites changed quintile in the air score. Almost all sites that changed quintile only changed by one quintile.

2. In the adapted ranking system the water pathway has a much greater relative weight than the air or general pathway: water:air:general = 10:5:4. When the relative weights are changed (by changing the multipliers) so that water, air and general have more equal weights (5:5:4), almost one third of sites (8) change one quintile in the water ranking and almost a quarter (6) change one quintile in the overall ranking. Changing the relative ranks so that water and air have equal weights and both weigh more than the general

category (5:5:2), 4 sites change one quintile in the air ranking and 6 in the overall ranking.

To summarise, the sensitivity analysis showed that overall scores of sites were relatively insensitive to exclusion of individual factors. Water and air scores were more sensitive to exclusion of factors, mainly because these scores are made up of less composite factors. The exclusion of some factors (e.g. waste quantity) can lead to a large proportion of sites obtaining a different scoring quintile although the difference is generally no more than one quintile. Changes in the relative weights of different pathways can also result in frequent changes in the ranking of sites. In the absence of knowledge about the relatively importance of different pathways contributing to a sites' exposure hazard, it is difficult to determine these weights.

Part B. Comparison with Expert Panel Scoring

Reasons for differences between the experts' scores and scores calculated using the adapted system were discussed a meeting with all four members of the expert panel. Table 2 summarises differences between the average of the four expert scores (after changes were made at the meeting) and scores from the adapted scoring system.

Table 2: Differences between quintile of the average expert score and quintiles of the adapted system score

number of score quintiles difference	*OVERALL*	*WATER*	*AIR*
	number of sites:		
0	12	8	6
1	5	10	7
2	7	4	8
3	0	3	4
4	1	0	0
total	25	25	25

The water and overall hazard categories show relatively good agreement between the experts and the adapted system with 18 and 17 sites (out of 25) respectively showing no or only one quintile difference. The coefficient for the correlation between quintiles of the expert scores and quintiles of the adapted system scores was 0.42 ($p=0.04$) for both overall and water hazard. Air hazard showed less agreement with more than one quintile difference for almost half (12) of the sites. This is also reflected in a very low correlation coefficient (0.07, $p=0.73$).

Differences in the two scoring systems occurred, in the experts' opinion, mainly because the adapted scoring system did not have 'links' between factors and did not take account of different types of waste. For example, a site that has had no biodegradable waste input does not generate landfill gas and does therefore not need a gas collection system. In the adapted scoring system the 'gas collection system' ranking factor for this site would be rated as 'high hazard' because no gas collection system is present. The experts however, would score this site as having a low air hazard because no gas is generated.

The experts felt that a scoring system based on a 'decision tree' structure would better reflect the complicated relationships between factors than the scoring system as adapted from the JRB system. They judged the expert scoring to be more valid than the adapted system since it did follow a 'decision tree', although not in a formalised way. They recommended further substantial adaptation of the JRB system, using the expert scoring as a 'Gold-Standard'. It was decided that rather than adapting the system to have a closer agreement with the expert scoring, the hazard potential classification would be based on the expert scoring.

Part C. Multipliers and Rating Scales in the Adapted JRB Ranking System

	RATING FACTORS	MULTIPLIERS	RATING SCALE LEVELS			
			0	*1*	*2*	*3*
	WATER					
1	**Distance to nearest public drinking water supply**	**7**	> 7 km	3 - 7 km	500 m - 3 km	< 500 m
2	**Distance to nearest surface water**	**4**	3-7 km	500 m - 3 km	100 - 499 m	< 100 m
3	**Depth to groundwater**	**8**	>=15 m	5-14.9 m	2-4.9 m	< 2 m
4	**Mean annual precipitation**	**4**	<= 700 mm	701-800 mm	801-900 mm	> 900 mm
5	Soil permeability	**8**	very low	low	medium	high
6	Evidence of water contamination	**5**	evidence for no contamination	weak evidence for contamination or no contamination	evidence from routine monitoring results	positive proof from in depth site investigation and reports
7	**Level of water contamination**	**7**	no contamination	low levels	moderate levels	high levels
8	**Type of water contamination**	**6**	no contamination	contamination restricted to soil and leachate within site boundaries or direct vicinity.	on-site contamination of groundwater or surface water; not known whether off-site water is polluted	widespread off-site contamination of ground water and/or surface water.
9	**Monitoring**	**4**	routine monitoring of leachate and on+off-site groundwater and/or surface water. monitoring of more than just basic substances	routine on-site monitoring of 3 media but only basic, or routine monitoring of 2 media of which 1 with more substances, or not routine monitoring of 3 media for more than basic substances	routine monitoring of only 1 media, or 2 media but no substances other than basics, or not routine monitoring of 1 or 2 media, or not routine monitoring of 3 media but no other substances than basics	no monitoring
10	Use of liners	**8**	100% lining since start (includes natural clay lining)	100% lining installed since start of operations but before study period, or 100% lining but unlikely to be intact	< 100% lining, or 100% lining but known to be breached	no lining
11	**Type of liners**	**4**	clay or other liner resistant to organic compounds (bentonite).	synthetic (man-made) or concrete liner.	asphalt liner, liner of granular/semi-permeable or in situ material.	no liner used
12	**Use of leachate collection system**	**6**	adequate collection and treatment of leachate since start	collection and treatment but only recent. collection and discharge to sewer. collection but not known how discharged	collection and recirculation. collection and discharge direct to water course.	no collection or treatment

Contd.

	RATING FACTORS	MULTIPLIERS	RATING SCALE LEVELS			
			0	*1*	*2*	*3*
	AIR					
13	**Evidence of air contamination**	5	evidence for no gas	weak evidence for contamination or gas or for no contamination/gas	evidence form routine monitoring	positive proof from in depth site investigation and reports
14	**Level of air contamination**	7	no contamination	low levels	moderate levels	high levels
15	**Type of air contamination**	6	no sign of gas/contamination	some gas on site	often/significant migration of landfill gas / other contamination on-site / some gas in vicinity and reports of smells	other contaminants detected off-site
16	**Monitoring**	4	routine on and off site gas monitoring / routine on and/or off-site gas and minor constituents	routine on site gas monitoring only.	monitoring but not routine	no monitoring
17	**Use of gas collection system**	6	collection and flaring, installed before study period	collection and venting, installed before study period	collection and flaring installed during study period	no gas collection during study period
18	**Daily cover**	4	newly added waste is covered daily, no reported problems	daily cover but problems reported: smells, wind blown litter	cover but not daily / daily cover but known to be inadequate	no covering of newly added waste
19	**Capping of inactive parts of site and closed/ abandoned sites**	4	cap applied to all completed parts of the site within 6 months, no reported problems	capping of most parts of site (>50%) / cap applied to all parts but reported problems / cap applied to all parts but after 6 months or time unknown	capping of some parts (<50%) / inadequate capping, known to be breached.	no cap applied
	GENERAL					
20	**Land within 3 km used for recreation or local food production**	4	no	food growing but not known whether local consumption / land used for recreational purposes	land used for local food production: allotments, fishing	land commonly used for both recreation and local food production
21	**Years since start of operations**	4	5-13 years	14-23 years	24-33 years	> 33 years
22	**History of site management**	4	site well managed: most measures to prevent off-site migration of chemicals taken	most measures taken but only recently or inadequately	only some measures taken	old, uncontrolled site: no measures incorporated to prevent off-site migration.
23	**Hazardous waste quantity**	8	volume: <=30,000 m3	volume: 30,000-100,000 m3	volume: 100-500,000 m3	volume: > 500,000m3
24	**Total waste quantity**	6	< 100,000 m3 < 10 hectare metres	100,000 - 500,000 m3 10 - 50 hectare metres	500,000 - 1,000,000 m3 50 - 100 hectare metres	> 1,000,000 m3 > 100 hectare metres

APPENDIX 9 : Landfill Site Ranking Questionnaire

EUROHAZCON LANDFILL SITE RANKING QUESTIONNAIRE

Site : _____

Instructions for completion:

- For all questions: best estimates/guesses better than nothing !!

- All questions apply to the year 1993 (for both operational and closed sites) unless otherwise stated. If you give answers/estimates for any other year please indicate this.

- Please enclose relevant documentation (in your own language) such as:
  - site plan (indicating monitoring points, completed areas, unfilled areas, etc.)
  - copy of the site license (obtainable from the site operator or from the waste regulation authority)
  - inspection reports; it would be important to have consecutive reports over a substantial period of time. For example if a site is inspected once a month, consecutive reports over 3-6 months in 1993 would be sufficient. Copies of such reports should be obtainable from the site operator or the authority that conducted the inspection (waste regulation authority).

- Important sources of information, apart from the site operator, may be:
  - local waste regulator (authority that gives out licenses and inspects the sites).
  - local residents complaints committee (some sites have a system for the reporting of local complaints),
  - local press office.

1. WASTE QUANTITY

1.1 Current area of site containing waste _____ ha

1.2 Total volume of waste in place at end 1993 _____ m^3
or
1.3 Total weight of waste in place at end 1993 _____ tons

1.4 Mean depth of waste at end 1993 _____ m

1.5 What is the total *expected* volume *at completion*?
_____ m^3

'Hazardous' waste quantity

1.6 Give the total weight or volume of **special/hazardous/toxic/notifiable waste*** in in place:

_____ m^3

_____ tons

or estimate the percentage of total waste in place which is **special/ hazardous/ toxic/ notifiable waste***:

_____ %

* as defined in the 1991 EC Directive on hazardous waste (see annex).

2. WASTE CHARACTERISTICS

For **all hazardous and industrial** waste present in the site:
Please describe *in as much detail as possible* what types of waste were disposed of, what industries this waste came from, which hazardous chemicals were present in the waste, etc. Please enclose a copy of the *site license* or any other documentation that can help us to find out what sort of waste was deposited in this site.

3. OPERATIONAL DETAILS

Containment

3.1 Percentage of site area with lining:

- engineered (man-made) lining _____ % of site area
- natural lining _____ % of site area
- no lining _____ % of site area
- other, please specify: _____ _____ % of site area

(these fields should add up to 100%)

if lining:

3.2 When was lining first put in place? 19_____

3.3 Is the lining known to be breached (damaged)?

- ❑ yes
- ❑ no

Covering

3.4 Was newly added waste covered daily during the study period?

- ❑ no covering
- ❑ daily covering
- ❑ covering but not every day, give frequency of covering : _____

if no, go to 3.6

if yes:

3.5 What type of covering was used?

- ❑ soil
- ❑ other, please specify: _____

Capping

3.6 Has a cap been applied to completed parts of the site ? (or whole site if closed site)

- ❑ no cap applied
- ❑ cap applied to some of the completed site (<50%)
- ❑ cap applied to most of the completed site (>50%)
- ❑ cap applied to whole area of the completed site

if no, go to 3.9

if yes:

3.7 What was the longest time between completion of any part of the site and its capping?

_____ weeks/months/years (circle relevant period)

3.8 What is the type of cap in place (there can be more than one type)?

- ❑ clay or similar natural material
- ❑ plastic/manmade material
- ❑ other, please specify: _____

3.9 Have there been any reports or complaints related to waste blowing over the perimeter fences, smells, hazardous vapours, etc.?

- ❑ yes
- ❑ no

if no, go to 4.1

if yes, go to 3.10:

3.10 Please enclose details of these reports / complaints: who reported, when. what was done about the complaints, etc. Enclose copies of inspection reports, reports of local complaints committees, etc.

4. LEACHATE

Collection

4.1 Is there an engineered leachate collection system in place?

- ❑ yes
- ❑ no

if no, go to 4.4

if yes:

4.2 When did the collection system become operational? 19_____

4.3 What is the form of leachate disposal/treatment (i.e. what happens to the leachate after collection)?

- ❑ direct to water course
- ❑ to sewer
- ❑ recirculation in the waste
- ❑ to leachate treatment plant for chemical/biological treatment
- ❑ other, please specify: _____

Monitoring

4.4 Is quality of the leachate within the waste monitored?

- ❑ not monitored
- ❑ monitored by boreholes
- ❑ collection system samples monitored
- ❑ other, please specify: _____

if no, go to 5.1

if yes,

4.5 Number of leachate monitoring boreholes: _____

4.6 Number of leachate samples per year: _____ samples/year

Please indicate the locations of the leachate monitoring points on a site plan.

4.7 What substances are determined (which chemicals do you measure) in the leachate? (if too much to write down here please enclose documentation: list of substances for example).

4.8 Please enclose leachate monitoring results. If available enclose an annual summary for 1993. If summary monitoring results are not available please enclose a random sample of individual reports for 1993 (for example 1 for each month).

5. SOIL

5.1 Give the average permeability of the soil type comprising the landfill *base*:

❑ very low	$< 10^{-7}$ cm/sec	clay, silty clay, unfractured rock.
❑ low	10^{-5} - 10^{-7} cm/sec	sandy clay, clay loam, silty clay loam, sandy clay loam; less permeable limestone, sandstone, dolomite.
❑ medium	10^{-3} - 10^{-5} cm/sec	loam, silt loam, silt; moderately permeable limestone, sandstone, and dolomite.
❑ high	$>10^{-3}$ cm/sec	sand, loamy sand, sandy loam, gravels, highly fractured rock.

5.2 Give the average permeability of the soil type comprising the landfill *sides*:

❑ very low	$< 10^{-7}$ cm/sec	clay, silty clay, unfractured rock.
❑ low	10^{-5} - 10^{-7} cm/sec	sandy clay, clay loam, silty clay loam, sandy clay loam; less permeable limestone, sandstone, dolomite.
❑ medium	10^{-3} - 10^{-5} cm/sec	loam, silt loam, silt; moderately permeable limestone, sandstone, and dolomite.
❑ high	$>10^{-3}$ cm/sec	sand, loamy sand, sandy loam, gravels, highly fractured rock.

6. GROUNDWATER

6.1 Depth to groundwater (measured vertically from the lowest point of the filled wastes to the highest point of the seasonal water table:

_____ metres

Monitoring

6.2 Is groundwater monitored in the vicinity of the site?

❑ no
❑ yes

if no, go to 6.7
if yes:

6.3 Number of groundwater monitoring boreholes: _____

6.4 Frequency of groundwater monitoring: _____ samples/year

Please indicate the locations of the groundwater monitoring points on a site plan.

6.5 What substances are determined (which chemicals do you measure) in the groundwater? (if too much to write down here please enclose documentation: list of substances for example).

6.6 Please enclose groundwater monitoring results. If available enclose an annual summary for 1993. If summary monitoring results are not available please enclose a random sample of individual reports for 1993 (for example 1 for each month).

Contamination

6.7 Has there been any groundwater contamination?

- ❑ never (i.e. samples have always shown background quality)
- ❑ occasional/minor contamination (go to 6.8)
- ❑ often/significant contamination (go to 6.8)

6.8 If contamination was found please describe in detail when this occurred, which pollutants were found, etc. (please enclose all relevant documentation):

Presence of groundwater sources for water supply

Public

6.9 Are there any *public drinking water* supply boreholes/extraction points present within 7 km of the landfill site?

- ❑ yes
- ❑ no

if no, go to 6.12

if yes:

6.10 What is the distance from the site to the *nearest* public water supply borehole ?

_____ km

6.11 What is the number of public supply boreholes within 3 km from the site ?

_____

Private

6.12 Are there any *private* supply boreholes present within 7 km of the landfill site?

- ❑ yes
- ❑ no

if no, go to 7.1

if yes:

6.13 What is the distance to the nearest private water supply borehole?

_____ km

6.14 What is the number of private supply boreholes within 3 km from the site?

_____

6.15 Indicate use of these private boreholes (more than 1 answer possible):

- ❑ drinking water
- ❑ agriculture/irrigation
- ❑ commercial/industrial

7. SURFACE WATER

7.1 Distance to nearest surface water body (in metres): _____ m

7.2 Type of surface water body:

- ❑ canal/stream/river
- ❑ lake or reservoir
- ❑ wetland, mire, or marsh
- ❑ sea or estuary
- ❑ other, please specify: _____

Monitoring

7.3 Is surface water in vicinity (3 km) of landfill monitored ?

- ❑ no
- ❑ yes

if no, go to 7.8
if yes:

7.4 Number of surface water monitoring points: _____

7.5 Frequency of surface water monitoring: _____ samples/year

Please indicate the locations of the surface water monitoring points on a site plan.

7.6 What substances are determined (which chemicals do you measure) in the surface water? (if too much to write down here please enclose documentation: list of substances for example).

7.7 Please enclose surface monitoring results. If available enclose an annual summary for 1993. If summary monitoring results are not available please enclose a random sample of individual reports for 1993 (for example 1 for each month).

Contamination

7.8 Has there been any surface water contamination?

- ❑ never (i.e. samples have always shown background quality)
- ❑ occasional/minor contamination (go to 7.9)
- ❑ often/significant contamination (go to 7.9)

7.9 If contamination was found please describe in detail when this occurred, which pollutants were found, etc. (please enclose all relevant documentation):

8. LANDFILL GAS

Migration control

8.1 Are there landfill gas control systems in place? (more than one possible)

- ❑ none
- ❑ collection and venting (controlled emission into air) of landfill gas
- ❑ collection and flaring (burning off) of landfill gas
- ❑ collection and utilisation (power generation)
- ❑ other, please specify: _____

8.2 When did the gas collection system come into place? 19_____

Monitoring

8.3 Is there monitoring for the presence of landfill gas?

- ❑ no
- ❑ on-site
- ❑ in the vicinity of the site
- ❑ both on and off-site
- ❑ other, please specify: _____

if no, go to 8.8

if yes:

8.4 Number of gas monitoring points _____

8.5 Frequency of monitoring: _____ samples/year

Please indicate the locations of the landfill gas monitoring points on a site plan.

8.6 What substances are monitored (which chemicals do you measure) in the landfill gas? Do you monitor for any minor constituents of the gas? (if too much to write down here please enclose documentation: list of substances for example).

8.7 Please enclose landfill gas monitoring results. If available enclose an annual summary for 1993. If summary monitoring results are not available please enclose a random sample of individual reports for 1993 (for example 1 for each month).

Migration of landfill gas

8.8 Has there been any migration of landfill gas?

- ❑ no sign of landfill gas beyond the site
- ❑ some landfill gas in vicinity of site
- ❑ often/significant migration of landfill gas
- ❑ other, please specify: _____

8.9 Have there been any reports or complaints about odours/smells from the landfill ?

- ❑ yes
- ❑ no

if no, go to 9.1
if yes:

8.10 Please give details of these complaints: who reported, when, what was done about the complaints, etc. Enclose copies of inspection reports, reports of local complaints committees, etc.

9. CLIMATE AND LAND USE

Rainfall

9.1 Mean annual rainfall in the area.
- this question applies to the local area where site is located, or otherwise smallest area for which data is available (district, county).
- if possible, give the average annual rainfall for years over the whole study period.
- please specify area and period over for which the average annual rainfall was given.

- average rainfall: _____ mm
- area: _____
- years: _____

Wind direction

9.2 What is the direction of the prevailing wind in the local area where the site is located?

- wind direction: _____

Land use

9.3 Land use for recreational purposes
Please indicate whether the land within the 3 km zone around the landfill site is commonly used for recreational purposes (e.g. park, sportsfield, etc.)

- ❑ no, 3 km zone is not commonly used for these purposes
- ❑ yes, 3 km zone is used for recreational purposes. Please specify the use:

_____

_____

9.4 Land use for food production
Please indicate whether food for local consumption is commonly produced in the 3 km zone around the landfill site (e.g. home grown vegetables, dairy farms, local fishing)

- ❑ no, 3 km zone is not commonly used for these purposes
- ❑ yes, food for local consumption is produced in this area. Please specify:

_____

_____

10. PUBLIC / MEDIA CONCERN

Has this site ever been the subject of concern for the local population ? If yes, please give a detailed report of the concern, when, why, what was done about it. Please enclose reports/ documentation. Sources of this type of information: local press office, local complaints committee, inspection reports.

11. POLLUTION INFORMATION

Any extra information about pollution of water, air, vegetation, etc., related to the waste site would be very welcome. Please enclose reports, documentation, etc. of contamination incidents. Source of information: inspection reports, local press office.

Thank you very much for completing this questionnaire. Please ensure all relevant documentation, specified on the front page of this questionnaire, is enclosed.

APPENDIX 10 : Hospital of birth by distance bands

Study area	*Hospital number*	*cases* *0-3 km*		*3-7 km*		*controls* *0-3 km*		*3-7 km*		*all bands* *cases*		*controls*	
1	461	3	33.3%	7	53.8%	1	4.8%	4	17.4%	10	45.5%	5	11.4%
	431	6	66.7%	5	38.5%	19	90.5%	19	82.6%	11	50.0%	38	86.4%
	479	0		1	7.7%	0		0		1	4.6%	0	
										$\chi2=$	12.61	p=0.006	
2	607	3	21.4%	7	35.0%	14	32.6%	11	44.0%	10	29.4%	25	36.8%
	461	6	42.9%	9	45.0%	9	20.9%	3	12.0%	15	44.1%	12	17.6%
	445	4	28.6%	4	20.0%	19	44.2%	10	40.0%	8	23.5%	29	42.6%
										$\chi2=$	8.64	p=0.034	
3	44	0		2	6.1%	0		0		2	3.2%	0	
	66	25	86.2%	30	90.9%	65	100.0%	59	100.0%	55	88.7%	124	100.0%
	72	0		1	3.0%	0		0		1	1.6%	0	
	73	3	10.3%	0		0		0		3	4.8%	0	
	74	1	3.4%	0		0		0		1	1.6%	0	
										$\chi2=$	14.55	p=0.006	
4	44	3	33.3%	2	33.3%	5	41.7%	2	11.1%	5	33.3%	7	23.3%
	66	6	66.7%	4	66.7%	5	41.7%	16	88.9%	10	66.7%	21	70.0%
	77	0		0		1	8.3%	0		0		1	3.3%
	not known	0		0		1	8.3%	0		0		1	3.3%
										$\chi2=$	1.391	p=0.708	
6	1	12	60.0%	30	50.0%	61	43.9%	10	47.6%	42	52.5%	71	44.4%
	2	8	40.0%	28	46.7%	78	56.1%	11	52.4%	36	45.0%	89	55.6%
	4	0		1	1.7%	0		0		1	1.3%	0	
	7	0		1	1.7%	0		0		1	1.3%	0	
										$\chi2=$	5.9	p=0.116	
7	1	0		1	3.5%	5	7.0%	0		1	2.4%	5	6.1%
	2	3	25.0%	5	17.2%	4	5.6%	0		8	19.5%	4	4.9%
	4	5	41.7%	15	51.7%	46	64.8%	10	90.9%	20	48.8%	56	68.3%
	6	4	33.3%	8	27.6%	16	22.5%	1	9.1%	12	29.3%	17	20.7%
										$\chi2=$	9.279	p=0.026	
9	17	0		1	2.3%	1	1.9%	0		1	1.5%	1	1.5%
	20	0		3	6.8%	0		0		3	4.5%	0	
	21	20	87.0%	36	81.8%	44	84.6%	12	80.0%	56	83.6%	56	83.6%
	29	2	8.7%	2	4.6%	0		0		4	6.0%	0	
	30	0		1	2.3%	7	13.5%	3	20.0%	1	1.5%	10	14.9%
	32	0		1	2.3%	0		0		1	1.5%	0	
	51	1	4.4%	0		0		0		1	1.5%	0	
										$\chi2=$	16.36	p=0.012	
10	17	0		0		1	0.8%	0		0		1	0.7%
	20	1	4.8%	21	18.0%	0		0		22	15.9%	0	
	21	18	85.7%	85	72.7%	99	80.5%	13	86.7%	103	74.6%	112	81.2%
	30	1	4.8%	5	4.3%	14	11.4%	0		6	4.4%	14	10.1%
	32	0	0.0%	5	4.3%	9	7.3%	1	6.7%	5	3.6%	10	7.3%
	34	1	4.8%	0		0		0		1	0.7%	0	
	48	0		1	0.9%	0		0		1	0.7%	0	
	212	0		0		0		1	6.7%	0		1	0.7%
										$\chi2=$	31.24	p=0.000	
11	17	0		0		0		1	2.6%	0		1	1.9%
	20	0		2	9.5%	1	6.7%	0		2	3.8%	1	1.9%
	21	1	3.1%	1	4.8%	0		1	2.6%	2	3.8%	1	1.9%
	48	31	96.9%	18	85.7%	14	93.3%	36	94.7%	49	92.5%	50	94.3%
										$\chi2=$	1.68	p=0.642	

Study areas 8, 16, and 17 : only one hospital per study area

Study areas 5, 12, 13, 14, 15, 18, 19, 20 : Hospital of birth not known for controls