The impact of environmental pollution on congenital anomalies

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Major congenital anomalies are diagnosed in 2–4% of births. In this paper we review epidemiological studies that have specifically looked at congenital anomalies as a possible outcome of community exposure to chemical exposures associated with environmental pollution. These include studies of drinking water contaminants (heavy metals and nitrates, chlorinated and aromatic solvents, and chlorination by-products), residence near waste disposal sites and contaminated land, pesticide exposure in agricultural areas, air pollution and industrial pollution sources, food contamination, and disasters involving accidental, negligent or deliberate chemical releases of great magnitude. We conclude that there are relatively few environmental pollution exposures for which we can draw strong conclusions about the potential to cause congenital anomalies and, if so, the chemical constituents implicated, to provide an evidence base for public health and clinical practice. A precautionary approach should be adopted at both community and individual level. In order to prevent congenital anomalies, one must reduce exposure to potential teratogens before pregnancy is recognized (*i.e.* preconceptionally and in the first few weeks of pregnancy). It is a challenge to develop effective strategies for preconceptional care within the primary care framework. Prenatal service providers and counsellors need to be aware of the uncertainties regarding environmental pollution when addressing parental concerns.

Introduction

In this paper, we review epidemiological studies that have specifically looked at congenital anomalies as a possible outcome of community exposure to chemical exposures associated with environmental pollution. The assessment of whether and to what extent environmental pollution causes birth defects in the population also draws on other evidence, principally toxicological data, data from animal studies, detailed exposure data, and human data from those occupationally exposed to high levels of the chemical. This review does not constitute a risk assessment including these sources of evidence.

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Congenital anomalies are part of a spectrum of adverse pregnancy outcomes that may be associated with exposure to environmental pollution. This spectrum also includes fetal death, including early spontaneous abortion, low birth weight associated with prematurity or intrauterine growth retardation, and neurodevelopmental effects that can only be detected in later infancy and childhood.

Environmental pollution can in principle cause congenital anomalies through preconceptional mutagenic action (maternal or paternal) or postconceptional teratogenic action (maternal). Preconceptional mutagenic effects may include chromosomal anomalies and syndromes as a result of new mutations. Postconceptional action, the main focus of this paper, depends on the precise timing of exposure: in embryonic and fetal development, each normal developmental process occurs during a specific period of a few days or weeks, and it is during this 'sensitive period' that exposure to a teratogenic agent may lead to an anomaly. Thus, a particular chemical may cause a congenital anomaly after exposure in, say, the sixth week of development, but exposure during the previous or succeeding week may have no effect, or an anatomically distinct effect. Where a child has more than one anomaly ('multiply malformed'), this may be because exposure has covered a number of sensitive periods for different congenital anomalies, or because exposure at one developmental stage has a number of different effects on organogenesis.

The majority of these sensitive periods occur during the first trimester of pregnancy, when most organogenesis occurs. Thus, as much organogenesis occurs before the pregnancy is even recognized, protection of the embryo cannot rely on actions taken once the woman knows that she is pregnant. Relevant preconceptional exposures may also have postconceptional effects, for example if these are indirect (*e.g.* effects on endocrine function) or if the chemical has a long biological half-life in the body (*e.g.* PCBs). The development of the brain remains subject to adverse influences well into the second trimester and beyond[1,2].

Limitations of the epidemiological literature

Registries of congenital anomaly report 2–4% of births with congenital anomaly, depending on inclusion criteria and ascertainment methods. Cardiac defects account for over one-quarter of all cases, limb anomalies one-fifth, chromosomal anomalies and urinary system anomalies each around 15%, central nervous system anomalies including neural tube defects 10% and oral clefts 7%[3]. The subgroups that have been most commonly singled out for specific study are neural tube defects, oral clefts and more recently cardiac defects and it is therefore unsurprising that these subgroups arise most commonly in reports of pollution-related effects.

Congenital anomalies are a heterogeneous group of many individually quite rare conditions, even within the subgroups mentioned above. When looking for associations between an environmental exposure and many individual congenital anomaly types, one can expect some nominally statistically significant associations by chance alone, but on the other hand low statistical power to detect true associations for any one congenital anomaly type. When individual congenital anomaly types are lumped together to increase statistical power, associations specific to one or two congenital anomaly types may be obscured, especially if groupings are not consistent with what is known of aetiologic and pathogenetic heterogeneity, and if the grouping results in diagnostic noise where well defined conditions are mixed in with variably diagnosed conditions. Many studies only have the statistical power to detect rather large increases in risk, and a negative result must be assessed in this context. On the other hand, some researchers do not declare the process of lumping and splitting of congenital anomaly types that lies behind their presentation of results. Grouping different types together only after seeing results on individual conditions has doubtful statistical validity.

Some progress has been made in identifying pathogenetically more homogeneous groups, such as defects related to vascular disruption or defects related to cranial neural crest cells, where different anatomical types can be combined[4]. There is also discussion as to whether isolated defects and multiple malformations are aetiologically distinct, *e.g.* whether an isolated neural tube defect should be grouped together with cases where a neural tube defect is associated with other malformations[5,6]. 'Sequences' are excluded from the category of multiple malformations, where one malformation is a consequence of or closely related to another, *e.g.* spina bifida with hydrocephalus or clubfoot should be analysed as spina bifida only.

Epidemiologic studies address the problem of variation in diagnosis and reporting of more minor anomalies with greater or lesser success. Most registries employ exclusion lists of 'minor anomalies' which although they may be of relevance to environmental exposures are too inconsistently diagnosed and reported to be useful in population studies[3,4]. However, some malformations range from major to minor forms where thresholds for diagnosis may vary and description of severity is often lacking, *e.g.* microphthalmia, microcephaly, polydactyly or syndactyly. Hypospadias has been of particular recent interest in this regard, since data from a number of areas in the world have shown increasing prevalence in the decades preceding the 1980s, along with a range of other male reproductive abnormalities (see next section). Hypospadias ranges from distal to proximal forms, the distal (glanular) forms being much more common, and it has been difficult to determine whether differences in prevalence between populations in time or geography are real or the result of changes in diagnosis and reporting of distal forms[7].

In the last few decades, the increase in prenatal diagnosis of congenital anomaly followed by termination of pregnancy has presented a particular challenge to epidemiologists. During the period 1995–99 for example, EUROCAT data from 32 European regions showed that 53% of spina bifida cases and 33% of Down Syndrome cases were prenatally diagnosed leading to termination of pregnancy[3], averages which range from 0% in some regions to over 75% in other regions. Since these proportions also vary over time and subregionally, it is important to include terminations of pregnancy following prenatal diagnosis in epidemiological studies, often requiring different sources of information for case ascertainment. The practice of prenatal screening has also brought forward the time of diagnosis of a range of internal congenital anomalies (cardiac and urinary system particularly) leading to increases in reported prevalence of these anomalies in recent decades[3], particularly in areas with more intensive screening.

Many embryos and fetuses with a congenital anomaly are lost as spontaneous abortions, and indeed many chromosomal anomalies are never seen at birth as the malformations are not compatible with continuing *in utero* life. Studies of congenital anomalies diagnosed prenatally or at birth focus on 'survivors' and it is possible that environmental exposures may act on the probability of survival of the malformed fetus, rather than causing abnormal morphological development itself. Although this caution is often raised (especially to explain surprising results such as a negative association between exposure and risk of malformation), direct investigation of such an effect is difficult and it has yet to be established that any environmental exposure acts on differential survival of malformed and normal fetuses. Another consequence of the fact that we analyse congenital anomalies only after a period of 'prenatal selection' is that as prenatal screening and diagnosis are carried out earlier in pregnancy, followed by termination in cases of severe anomaly, so registries of congenital anomalies will pick up cases which would otherwise have been lost as unrecorded spontaneous abortions, particularly for conditions such as Down Syndrome where spontaneous fetal death rates are particularly high. This can introduce artefactual differences in prevalence over time and between areas.

Where teratogenic (malformation causing) effects are concerned, it is usually assumed that there is a threshold of exposure below which the exposure is insufficient to overcome the natural regulatory and repair mechanisms during fetal development and therefore will not lead to a major malformation[8]. This contrasts with the stochastic model for cancer initiation, where ever-smaller doses are simply associated with ever-smaller probabilities of effect and a linear dose–response curve is often adequate. Especially where there is evidence from occupational or animal studies that high dose exposures can be teratogenic, the relevant question is whether chronic low-level pollution reaches the threshold for effect. Biologically, it is reasonable to assume that each individual has their own

threshold which an exposure would need to exceed to lead to major disturbance of development. Epidemiologically, it is reasonable to assume that individuals have different thresholds, depending on co-existing or previous environmental exposures as well as genetic susceptibility. Epidemiologic studies determine whether the environmental exposure is sufficient to exceed the thresholds of a significant proportion of the population. Under this model, it is important not to engage in the 'averaging' of exposure used for cancer epidemiology, *i.e.* the distribution of exposure dose in the population matters, and duration may have importance independently of total dose. Thus, the effects in a population with uniform medium exposure may differ from the effects in a population with the same average exposure but where some are unexposed and others highly exposed. This is relevant to the type of exposure modelling one might undertake. For example, wind direction may be important in determining which areas near a factory have the highest average exposure (it may be that further residents downwind experience higher average exposure than nearer residents upwind), but maximum exposure may occur on windless days near the factory and affect all those living closest to the source regardless of wind direction.

If one establishes that an environmental pollutant is causing congenital anomalies, then the next relevant question is usually what genetic and other environmental factors interact with exposure such that only the minority of exposed pregnancies are affected (or why only the minority of individual thresholds have been exceeded). Low periconceptional folate status is now a well-established risk factor for neural tube defects and possibly a much wider range of anomalies[9]. A study of trihalomethane exposures in drinking water looked for (but did not find) interactions with MTHFR genotype, a folate related gene, after suggestions that adverse effects of consumption of water with high trihalomethane levels was restricted to women not taking periconceptional folic acid[10]. Other genes of potential interest are those involved in detoxification of xenobiotics. If genetic susceptibility to the effects of the pollutant is rare, classic epidemiological approaches are unlikely to detect an increase in risk at the population level.

Exposure assessment for studies of environmental pollution is often poor, as discussed elsewhere in this volume. Frequently, measures such as residence near a potentially polluting source are taken as surrogates for exposure rather than a more direct individual measure of exposure, and such measures may relate to the time of birth rather than organogenesis. Poor exposure measurement reduces the power of studies to detect true pollution related effects and the size of the observed risks. One particular problem is that environmental pollution often constitutes a mixture of chemicals, and we may not be sure which constituents to measure in relation to their health effects, or whether indeed the interaction of constituents

is important. This also means that it is difficult to assess 'similarity' between communities exposed or potentially exposed to environmental pollution, and thus to assess whether the body of evidence relating to any particular type of pollution suggests an impact on congenital anomalies or not. 'Inconsistent' studies may be inconsistent not only because of statistical noise related to low statistical power or different sources of bias, but the fact that they are investigating different exposures either qualitatively or quantitatively. Moreover, the epidemiological method depends on there being relevant variation in exposure in the population and a study may well be 'negative' if the range of exposures in the study population is so narrow that differences in resulting risks are small, even if the exposure is causally related to congenital anomaly risk.

Environmental epidemiological studies are observational, not experimental, and as such open to 'confounding'. A 'confounder' is a factor associated with both the health outcome (congenital anomalies in this case) and the exposure (environmental pollution). Typically, for example, people of lower social status are more highly exposed to pollution, either because they move where housing prices are lowest, have less power or advocacy skills to prevent exposure, have less access to environmental health information, or because aspects of lifestyle associated with greater deprivation (such as ability to buy bottled water) lead to higher exposure. Although information on the extent to which congenital anomaly prevalence is linked to social status is rather limited, current evidence does suggest that more socio-economically deprived groups have higher non-chromosomal congenital anomaly rates[11], and part of this may be explained by nutritional status. Thus we have to take this into account when interpreting an association between, for example, residence near an incinerator and a raised prevalence of congenital anomaly, as a causal effect of incinerator releases. Since, when assessing environmental pollution, we are usually interested in fairly small increases in risk affecting large numbers of exposed people, socio-economic confounding is a particular problem. Chromosomal anomalies such as Down Syndrome are strongly related to maternal age, and since at present average maternal age increases with social status, higher social status is associated with a greater risk of a Down Syndrome affected pregnancy reversing the direction of socio-economic confounding.

There is a tendency for the sceptical to dismiss observational studies on the basis of uncontrolled confounding, but it is difficult to come up with other realistic strong confounding scenarios for congenital anomalies in relation to established risk factors. Maternal age is strongly related to gastroschisis (young maternal age), and to Down Syndrome and related abnormalities (older maternal age), but not to other non-chromosomal anomalies[3]. Occupational risks and drug related risks are unlikely to have a significant effect at population level as the proportion of the maternal population exposed is small. Differences in folate status are possible

between groups exposed and unexposed to environmental pollution, though control for differences in socio-economic status may deal with such differences quite well. Smoking is not a well-established risk factor for congenital anomalies, although it may play a role for specific anomalies.

The scientific and public health literature can be divided into papers pursuing an *a priori* defined hypothesis about a particular pollution source, and studies responding to clusters of congenital anomalies with a suspected local environmental cause. Reports in the media of a 'cluster' of birth defects, often associated with suspected local contamination of air or water, are relatively frequent and may result in a public health investigation. A random distribution of cases in space and time is not a regular distribution, and there will be patches of denser concentration of cases. A community may become aware of an aggregation of cases in their area, and seek the nearest reason such as a waste site or power line. The problem has been likened to the 'Texan sharpshooter' who draws his gun and fires at the barn door, and only afterwards goes and draws the target in the middle of the densest cluster of bullet holes. Since random 'clusters' are expected to occur and there are usually few cases for investigation, some argue that the likelihood of finding a common causal factor is so low that it may often be better not to investigate but instead to 'clean up the mess' of the suspected contaminant without demanding causal proof[12]. Others have tried to derive guidelines for deciding which clusters are worth investigating. Nevertheless, distinguishing random clusters from clusters with a true local environmental cause has proved a generally intractable problem.

Sources of pollution and their impact on congenital anomalies

We have based this section on a Medline and BIDS review, limited to publications in the English language. Space does not permit us to describe or fully reference the studies identified, but the full review is available on request to the authors. We chose to focus in this paper on exposures which have been the subject of a larger number of studies or larger studies (multi-community or multi-site studies), and additionally mention some smaller single community studies which have been particularly influential in creating awareness of the potential impact of different types of environmental pollution. In this way we also seek to avoid the problem of publishing bias, where smaller studies are more likely to be published (and therefore reviewed) if they have positive results.

Most of the relevant epidemiological studies are either case–control studies (where a group of cases with congenital anomaly are compared to a group of controls without, seeking to answer whether a greater proportion of

cases than controls have a certain risk factor present) or ecological studies (where in each population subgroup, the frequency/intensity of one or more risk factors is measured, as well as the frequency of birth defects, seeking to answer whether population subgroups with higher levels of a risk factor also have a higher proportion of affected births). Especially where environmental pollution is the subject of study, it cannot be assumed that a case–control study provides better evidence than an ecological study. For example, a case–control study may use as its exposure measurement for each study subject zonal drinking water measurements, and differ little from ecological studies based on these same measurements, except where more detailed individual information on confounders is sought. Difficulties in achieving unbiased control selection are avoided by ecological studies based on all births in the population. On the other hand, it should be clear from the discussion above that there are many reasons why reported prevalence of congenital anomalies may differ between areas, other than environmental exposures, and interpretation of ecological studies should recognize this. Consistency of results between different types of study with different types of bias helps interpret association as causation[13].

Studies of large-scale geographical differences or temporal trends in congenital anomaly prevalence are rarely able to overcome difficulties of interpretation related to differences in diagnostic criteria and ascertainment methods between populations. The higher prevalence of neural tube defects in UK and Ireland compared to the rest of Europe, and the strongly declining total prevalence of neural tube defects (including terminations of pregnancy following prenatal diagnosis) during the 1960s to 1980s in UK and Ireland are however well established phenomena[3,14], possibly related to nutritional factors. The reported prevalence of congenital heart disease and some internal urinary system anomalies has been increasing in Europe in the last two decades, but much of this may be explained by earlier and better diagnosis of these conditions as previously mentioned and against this background it would be difficult to discern exposure-related trends. A worldwide increase in the prevalence of gastroschisis, a rarer anomaly, is without explanation[15]. Recent interest in relation to environmental pollution has focused on the possibility that male reproductive abnormalities, hypospadias and cryptorchidism, have been increasing in prevalence in the decades preceding the 1980s, along with a range of other male reproductive system health outcomes[16]. The difficulty in interpreting hypospadias trends has been mentioned above. Although the evidence for the increasing trends in most of the outcomes is disputed, the possibility that all of these apparent increases are related to increasing exposures to endocrine disrupting chemicals in the environment (present in many of the categories of pollution we discuss below such as pesticides, waste releases and industrial releases) is an active and important area of present research.

Drinking water contamination

Inorganic contaminants in drinking water studied in relation to congenital malformation risk include heavy metals (lead, cadmium, arsenic, barium, chromium, mercury, selenium, silver) other elements, nitrates, nitrites, fluoride and water hardness.

Whereas detailed studies have established beyond doubt the neurotoxic effects of pre- and postnatal lead exposure on children, there is much less evidence concerning the risk of congenital anomalies[17,18]. Two recent studies report conflicting results in relation to neural tube defects and lead in the water supply[19,20], and an Italian study reported a positive association between lead pollution emitted by ceramic factories and the prevalence of cardiovascular anomalies, oral clefts and musculoskeletal anomalies[21].

Large differences in the prevalence of neural tube defects in the British Isles gave rise in the 1970s to theories that the hardness of local water supply could be responsible for this difference. Water hardness is a measurement of total calcium and magnesium levels of the water. This theory was tested in several studies[22,23]. Generally, associations between rates of neural tube defects and water hardness reported in ecological studies have not been substantiated by case–control studies.

In Australia, reports of a high incidence of perinatal mortality due to congenital malformations in one district led investigators to study the local water supply of that area. Nitrates were found to be high in the drinking water in this area, especially in groundwater sources. A case–control study[24] reported an increased risk of congenital malformations for those consuming groundwater and for those consuming water with high levels of nitrates. The nitrate association showed a dose–response effect, supportive of a causal interpretation. Risks for central nervous system and musculoskeletal defects especially were raised for mothers consuming water from groundwater sources. Some subsequent studies have been supportive of a potential effect of high nitrate levels on central nervous system defects[25], anencephaly but not spina bifida[26] and cardiac defects[27].

Early reports in the 1950s suggested that fluoridation of water supplies might result in an increase in the frequency of Down Syndrome. A subsequent comparison of overall Down Syndrome rates in fluoridated and non-fluoridated areas in Massachusetts found no evidence for a difference[28]. Analysis of data from 51 American cities also found no difference in maternal age-specific Down Syndrome rates between fluoridated and non-fluoridated areas[29].

Chlorinated and aromatic solvents (trichloroethylene, benzene) have entered drinking water from leaking underground storage tanks, landfill, and other waste disposal facilities; for example 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 childhood leukaemia. Lagakos *et al*[30] 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 of leukaemia was confirmed and the pregnancy outcome survey found associations with eye/ear congenital anomalies and central nervous system/oral cleft/chromosomal anomalies (mostly Down Syndrome).

Chlorination by-products are halogenated solvents, predominantly trihalomethanes (THM): chloroform, bromodichloromethane, dibromochloromethane and bromoform. The evidence is growing that chlorination by-products may be associated with poor pregnancy outcome[31,32]. Studies of congenital anomalies have reported a range of associations between specific measures of chlorination by-products and specific anomalies, including NTD, oral clefts, cardiac anomalies and urinary tract defects but it is not yet clear which of these represent causal associations[27,31,32].

Waste disposal (landfill sites and incinerators) and contaminated land

Routes of exposure to landfill sites may be through drinking water (see above), other contact with contaminated water, releases to air or contaminated soil. 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[33]. Love Canal, New York State, brought the world's attention to the potential problems of landfill and contaminated land. Large quantities of toxic materials (residues from pesticide production) were dumped at the landfill 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. 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 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. A subsequent study interviewing parents reported an increase in birth defects[34].

Sosniak *et al*[35] investigated the risk of adverse pregnancy outcomes for people living within 1 mile of a total of 1281 NPL sites in USA. 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.

Geschwind *et al*[36] investigated the risk of congenital malformations near 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, musculoskeletal 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 musculoskeletal) and living near a hazardous waste disposal site[37]. 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 2 years of this study were also included in Geschwind's study, and two more years were added. Marshall *et al*'s[37] attempts 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 were limited by small numbers of cases in each exposure subgroup.

A study by Croen *et al*[38] in California 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 (two-fold) and heart defects (four-fold) were increased for maternal residence within a quarter mile of a site although numbers of cases and controls were too small (between two and eight) 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 military-base residents with NTD-affected pregnancies being more likely to deliver in non-military hospitals than military-base residents with unaffected pregnancies. A subsequent study

focusing on ethnic minority infants in California found some small increases in risk of congenital anomaly, although not statistically significant[39].

A European multi-site study reported a 33% increase in risk of all non-chromosomal birth defects combined for residents living within 3 km of 21 hazardous waste landfill sites in 10 European regions[40]. Neural tube defects and specific heart defects showed statistically significant increases in risk. Socio-economic confounding did not readily explain the results. A second part of the study reported a similar increase in risk of chromosomal anomalies (OR 1.41, 95% CI 1.00–1.99)[41]. The study included both open and closed sites that ranged from uncontrolled dumps to relatively modern controlled operations. 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 the risks. There was little indication that risk of congenital anomaly was associated with an agreed ranking of the hazard potential of the sites[42].

A study of all landfill sites in England, Scotland and Wales, investigated the risk of congenital malformations, and low and very low birth weight outcomes in populations living within 2 km of a landfill site, open or closed[43]. The study included over 9000 landfill sites. The study found that 80% of the population of Great Britain lived within 2 km of a landfill site. Statistically significant but small (<10%) increases in risk were reported around all sites combined for all congenital anomalies, neural tube defects, hypospadias, abdominal wall defects, and low birth weight. Findings for sites that were licensed to take special (hazardous) waste were generally similar to non-special sites. In this study, only 20% of the country was available as reference population and the comparability of the 'landfill' and 'reference' areas therefore raises questions. Also, if risks were associated with a particular group of 'high-risk' landfill sites such a finding would be lost in the overall comparison of over 9000 sites in this study. Excess risks of some specific anomalies were found in the period before the opening of the landfill sites in the subgroup of sites that opened during the study period.

There has been very little epidemiological study of the risk of congenital malformation or any other pregnancy outcome in populations living near incinerators. Incineration uses controlled combustion to dispose of a wide range of wastes. Airborne pollutants of concern for health impacts include a wide range of inorganic compounds (CO, NO_x, SO_x, HCl); heavy metals, specifically cadmium, lead, mercury, chromium and arsenic; and organic compounds specifically dioxins and furans, polychlorinated biphenyls (PCBs), and polycyclic aromatic hydrocarbons (PAHs)[44]. Incinerators with modern combustion design, practices and air pollution control equipment generally show much reduced emissions compared to old, uncontrolled incineration facilities. A multi-site study using births data from

1956 to 1993 in Cumbria, UK, found excesses in perinatal and infant mortality due to spina bifida and heart defects near incinerators, after controlling for social class[45].

Pesticides in agricultural areas

Non-occupational human exposure to pesticides can occur through domestic use in homes and gardens, consumption of treated foodstuffs, contaminated drinking water, or residence in agricultural areas associated with contaminated air, water or soil. The possible teratogenic effects of pesticides in humans have long been the subject of controversy. Reviews of pesticides and congenital malformations and other pregnancy outcomes have been published elsewhere[46–48]. Studies of residential exposure to pesticides have used proxy measures of exposure such as pesticide usage in the area of residence, residence in or near pesticide application areas, or residence near agricultural crops. A number of positive studies exist relating to residential exposure to agricultural usage, but it is difficult to arrive at any conclusions owing to the wide variety of pesticides and congenital anomalies studied, so that few studies can be compared or combined. An effect of environmental exposure is consistent with growing evidence that occupational exposure to some pesticides may be teratogenic.

Air pollution and industrial pollution sources

There are hardly any studies of the association between ambient air pollution (particulates, sulphur dioxide, nitrogen oxides, carbon monoxide) and the risk of congenital malformation despite growing evidence of a relationship with other pregnancy outcomes such as low birth weight and infant mortality. One recent study reports an increase in risk of cardiac defects, including ventricular septal defects, in relation to carbon monoxide exposure in California[49]. Odds ratios of around 3 were found comparing the lowest with the highest quartile of CO exposure during the second month of pregnancy. There were no relationships with NO_2, ozone, or PM_{10}. Orofacial clefts showed no relationship with any of the pollutants. Other birth defects were not studied.

The Brazilian town of Cubatao is reported to be one of the most polluted in the world. A study[50] compared the rate of congenital malformations in Cubatao with reference rates from a congenital anomaly registry network covering 102 hospitals in South America. A higher than expected prevalence rate was found for polydactyly only.

Five studies have investigated the risk of congenital malformation, in particular central nervous system defects, in areas where PVC polymerization plants were located in the USA and Canada because of prior

concern about the potential teratogenicity of vinyl chloride[51–56]. Taken as a whole, these studies have not been able to establish a convincing relationship between residence near the plants and the congenital anomalies studied.

Since there is such a variety of industrial pollution, and so little existing evidence regarding its impact, one approach has been to first take a broad brush look at the impact of industrial pollution in general. Shaw *et al*[57] carried out a multi-site 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. A 1.5-fold increase in risk was found for heart and circulatory malformations in the areas classified as having potential human exposure to such sites. Results were not adjusted for socio-economic status. A study of perinatal and infant mortality due to congenital anomalies in Cumbria, UK found no evidence of any increase near hazardous industrial sites, these sites not including landfills or incinerators[58].

A study following up suggested risks of residence near landfill sites found instead increased risks related to residence near solvent and metal emitting sites[37]. A number of specific types of factory or industry have been studied in a single community only. Some of these have found increased prevalence of congenital anomaly, but the evidence is insufficient to draw a causal interpretation.

Contamination of food

Contamination of food (as opposed to component nutrients or the use of preservatives) has been little studied in relation to congenital anomalies. One of the principal areas of current interest is organic mercury and persistent organochlorines in fish. Following disasters involving mercury contamination (see next section) it is known that damage to the fetal brain and microcephaly can result from high exposures[59]. Levels of mercury found in fish have been of concern and led to advice[60] to limit intake of tuna, shark, swordfish and marlin during pregnancy. Epidemiologic studies of adverse effects of *in utero* fish consumption have focused on neurodevelopmental effects rather than the morphological brain anomalies themselves, and brain anomalies would tend to be under-diagnosed and under-ascertained by congenital anomaly registers. A Swedish study found no difference in malformation and fetal death rates[61] between fishing communities on the east coast of Sweden where pollution with persistent organochlorine compounds including PCBs is high, and fishing communities on the west coast where such pollution is low.

Disasters involving environmental pollution

Up to now, we have been reviewing environmental pollution corresponding to normal licensed industrial and agricultural practice, although it is of course possible and even likely that substandard practice exists leading to more pollution than would ordinarily be predicted, either associated with chronic releases or undeclared accidents. We now briefly review some situations that can be classified as 'disasters' involving accidental, negligent or deliberate chemical releases of great magnitude, where there have been subsequent studies of congenital anomalies in the affected population. These studies are not only of interest in relation to the risks associated with such releases, but also shed some light on the risks associated with the chemicals involved for use in risk assessments relating to lower dose environmental exposures.

Methyl mercury is an established teratogen. Mercury poisoning during pregnancy in residents around the Minamata bay in Japan (1953–1971) caused central nervous system anomalies in new-borns[59,62]. Infants born to exposed mothers showed a complex of neurological symptoms, including cerebral palsy, ataxia, disturbed psychomotor development and mental retardation sometimes accompanied by microcephaly. The mothers did not show symptoms. In Iraq (1971–72), grain treated with methyl mercury was consumed by local populations and hundreds of people died from mercury poisoning. Brain damage and neurological effects were found among the infants exposed *in utero*[59,63].

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 in 1968. Apart from PCBs, other contaminants like furans were found in the rice oil. Among 13 exposed mothers, who all had the Yusho disease, two stillbirths were reported and babies were born with skin stains (cola-coloured babies), conjunctivitis and neonatal jaundice[64]. All live born babies were also below the mean weight for gestational age. After poisoning of cooking oil with PCBs (contaminated by dibenzofurans) in Taiwan in 1979, similar effects were noted: exposed children were shorter and lighter, and had skin, nail and teeth anomalies[65]. One study reported a very high rate of infant death in babies who had been born with hyperpigmentation (8/38, 20.5%)[66].

In 1976, an accident at a factory producing trichlorophenol released a cloud of toxic materials including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the area of Seveso, Italy. The quantity of TCDD released into the environment was large but was never precisely determined. The prevalence of chloracne (an acute effect of exposure) was high in residents in the area immediately surrounding the factory, zone A, and lower but still raised in two areas with low and very low exposure, areas B and

R. Mastroiacovo *et al*[67] studied birth defects in the Seveso population up to 5 years after the accident. A total of 26 babies were born in zone A, none of which had major malformations, two of which had minor defects. Rates of major malformations in zone B and R were similar to those in a control area. The number of births in the highly exposed area was too small to draw firm conclusions about anything but the absence of very high absolute risks.

Agent Orange is a mixture of 2,4-D and 2,4,5-T sprayed by the US military in Vietnam as a defoliant to aid military manoeuvres, and thus exposing residents of those areas. Evidence for adverse reproductive effects of dioxins, Agent Orange and phenoxy herbicide spraying have been reviewed[68–71]. Two types of studies were carried out: studies of reproductive outcomes in couples who lived in areas that were sprayed with Agent Orange and studies of Vietnamese, American and Australian soldiers who served in South Vietnam, which in the context of this review of non-occupational exposures may serve as an indicator of community exposures of Vietnamese residents, though mainly limited to the potential for paternal preconceptional mutagenic effects. Rates of birth defects reported in the studies of Vietnamese residents were low compared to those found in Western countries, raising concerns about completeness of ascertainment. Although the quality of the studies is difficult to judge, they do report increased risks of miscarriages, stillbirths, molar pregnancy and birth defects in residents of the sprayed areas. Some increases in prevalence of specific congenital anomalies in offspring of fathers who served as soldiers were observed but no overall increase in anomalies and no clear dose–response relationship with dioxin exposure.

A study in north Cornwall examined outcomes of pregnancy after an incident where aluminium sulphate was added to the local water supply accidentally[72]. Ninety-two pregnancies in the affected area during the contamination incident were compared to pregnancies in the area before the incidents and pregnancies in an unexposed area. The study reports no excess of perinatal deaths, low birth weight, preterm birth, or congenital malformation in the affected area. There was however an increased rate of talipes among the exposed pregnancies.

In a Hungarian village, 11 out of 15 live births in a 2-year period were affected by congenital abnormalities and six were twins[73]. Four out of the 11 affected children had Down Syndrome. Trichlorofon (an organophosphate pesticide) was used in excess at local fish farms, and local people were known to have eaten the local fish. No congenital abnormalities occurred in the 2 years after the chemical treatment of fish was banned. The study did not manage to establish a full explanation for the cluster of congenital anomalies in terms of fish consumption, but the evidence was suggestive that Trichlorofon was at least a partial explanation.

Implications for clinical and public health practice

There are relatively few environmental pollution exposures for which we can draw strong conclusions about the potential to cause congenital anomalies, and, if so, the chemical constituents implicated, to provide an evidence base for public health and clinical practice. We lack a coherent surveillance strategy for licensed agricultural and industrial processes, and are necessarily in an even poorer position in relation to illegal practices. There is however enough evidence for the prevention of congenital anomalies to figure strongly among the health-related arguments reviewed in this volume for taking a precautionary approach and implementing measures to reduce community exposures to environmental pollution. High-risk groups with maximum exposure should in particular be identified.

Environmental pollution is almost by definition a by-product of agricultural and industrial processes in which we engage to increase our health and welfare, and there is therefore a balance between risks and benefits at both community and individual level. At community level, it is relevant to ask whose health and welfare is being improved, and who is suffering the negative consequences, and thus whether the benefits and risks are fairly distributed. At individual level, balancing decisions must also be made—for example, it might be counterproductive to limit intake of fresh fruit and vegetables in order to avoid pesticide exposure (although measures such as washing and peeling can be encouraged), or to limit recreation and exercise through swimming, walking or cycling in order to avoid exposure to contaminants of air and water.

In terms of clinical practice, one needs to tread a fine line between false reassurance and false alarm when counselling a future or current parent on the basis of current evidence. 'Absence of evidence is not evidence of absence'. It needs to be clear to parents that mechanisms are not necessarily in place to protect them against teratogenic exposures, especially weaker teratogenic exposures. A wise approach is to reduce personal exposure to environmental pollutants where possible and also to reduce personal exposure to chemical exposures in the home and garden. Periconceptional folic acid supplementation, one of the very few known preventive measures, can be advised both to reduce overall risk of congenital anomaly and also possibly to protect against risks associated with specific environmental exposures, although there is as yet little evidence to support this interaction. However it should be emphasized that the prevalence of major congenital anomalies is approximately 2% of births (or 2 in 1000 births for neural tube defects, and 2 in 10,000 for gastroschisis) and thus, even in relation to a doubling of risk, an exposed pregnant woman is still unlikely to have a child affected by a major congenital anomaly. Estimations of risks related to residence near landfill sites have for example been less than 1.5-fold.

Environmental concerns should be incorporated into both preconceptional and prenatal care. In order to prevent congenital anomalies, one must reduce exposure to potential teratogens before pregnancy is recognized (*i.e.* preconceptionally and in the first few weeks of pregnancy). This should be one part of the public health function in primary care. Targeting women preconceptionally has been found to be poor in another area of congenital anomaly prevention, periconceptional folic acid supplementation[74]. It is a challenge to develop effective strategies for preconceptional care within the primary care framework. Many women go on to have more than one child, and community midwives and health visitors are already ideally placed, as part of interagency working and with appropriate training, to give environmental health education and to refer at risk families for specialist interventions. Important opportunities are currently being missed even in regard to well-known environmental hazards, for example to verify that domestic water has low lead levels. Relevant prenatal services include prenatal screening and prenatal counselling. Prenatal service providers and counsellors need to be aware of the uncertainties regarding environmental pollution when addressing parental concerns.

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