Saturday 18 August 2001

BMJ

Does exposure to landfill waste harm the fetus?

Perhaps, but more evidence is needed

Papers p 363

In this issue Elliott and colleagues report on the risks to fetuses associated with residence near landfill sites: they compared pregnancy outcomes among British women living within 2 km of any of 9565 landfill sites operational between 1982 and 1997 with outcomes among those who lived at least 2 km away from all known sites (the reference area).[1] They found excess risks for some adverse pregnancy outcomes, a finding consistent with previous literature, but a clear pattern of excess did not emerge and the excesses were small enough (generally less than 10%) that they could be due to study bias, a problem that is difficult to rule out in this type of study. Therefore, the question whether these results represent a causal connection between residential exposures to landfill and adverse outcomes is unresolved.

The authors found that 80% of the British population lives within 2 km of a current or closed landfill site. This remarkable finding has several implications. Firstly, it suggests that even small excess risks near landfill sites would be important in public health terms. Secondly, it raises the question of whether the reference population is unusual, and thus whether the landfill and reference areas were comparable in terms of other risk factors for adverse birth outcomes—for example, poor nutrition. Thirdly, the main study findings relate to the risk of living near any sort of site, while the potential for harm may vary greatly between sites. Higher risks associated with a small number of sites could be lost in the overall comparison.

This large study, based on about eight million pregnancies between 1983 and 1998, was made possible through the use of postcoded national databases such as birth data and the National Congenital Anomaly System. Postcoding provided a means not only of measuring distance of residence from landfill sites but also of addressing comparability of the two populations in terms of other risk factors for adverse outcomes. It was found that 34% of the landfill area and 23% of the reference area were in the most deprived third of the Carstairs deprivation index—a classification of areas based on social class, unemployment, access to a car, and overcrowding. All analyses were adjusted for this difference; however, it cannot be assumed that the three category Carstairs index is an adequate proxy measure for all underlying risk factors. Failure to account for an unmeasured risk factor could have artificially inflated or deflated the relative risks for the landfill versus reference areas. For example, an absolute difference of 10% in the prevalence of a factor that doubles risk could increase or decrease the relative risk for landfill versus reference areas by around 5-9%.

Residence near a landfill site and excess exposure to hazardous chemicals cannot be assumed to be equivalent. There is little published information about the likely exposure concentrations for nearby residents,[2] although local authorities may have carried out risk assessments.[3] Contamination of water or soil may affect a much wider population, and the impact of air dissemination may depend on prevailing winds. Thus, if there is substantial exposure of the population, some of the more exposed people will live more than 2 km away, and some of the less exposed within 2 km. Furthermore, since the study was based on residence at pregnancy outcome, misclassification could occur because women moved home between the critical time window for exposure[4] and the end of pregnancy. Misclassification in terms of exposure or residence would tend to cause underestimation of differences in risk between landfill and reference populations.

Underreporting by district health authorities of anomalies among live born and stillborn children to the National Congenital Anomaly System is well known, and data on terminations of pregnancy for congenital anomaly were available to the study only from 1992. Underreporting might explain why in this study the prevalence of children needing surgical corrections for abdominal wall defects was 40 per 10 000 births whereas the reported prevalence of these anomalies at birth or termination was only 26 per 10 000. The important question here is whether reporting levels for anomalies would have differed systematically between the landfill and reference areas, thereby biasing the results.

Uncertainty about the meaning of epidemiological results, because of potential bias, is not resolved by arguments about statistical significance. In any case, the 99% confidence intervals quoted in the paper are too narrow since there was no allowance for sampling error in the reference population. However, some types of epidemiological comparison offer a stronger basis for inference than others. Evidence of an exposure-response relationship—whereby risk increases with increasing (markers of) exposure—can be convincing. Unfortunately, further classification of the landfill group according to distance from sites (such as <1 km and 1-2 km) was not carried out; the authors felt that inaccuracies in the recorded location of some sites would undermine this. An alternative approach that compared sites licensed to receive hazardous waste

BMJ 2001;323:351–2

and the remaining sites is probably not helpful in this regard if, as the authors suggest, the former sites were subject to stricter design and management.

A final set of comparisons concerned the area surrounding the 5260 sites that opened in the study period: relative risks for the population of this area compared to the reference area were calculated both before and after the new sites opened. For most outcomes the relative risks (landfill *v* reference) decreased after opening or remained the same. The exceptions were low birth weight and neural tube defects, for which the relative risks increased by 6% and 7% respectively. These comparisons offer an alternative assessment of the influence of landfill sites on risk without entirely solving the problems mentioned above.

It is important that we gain a better understanding of the health impact of different waste management options. Future studies ought to give attention to better estimates of the exposure of residents.

R McNamee *senior lecturer in medical statistics*

School of Epidemiology and Health Sciences, University of Manchester, Manchester M13 9PT

H Dolk *professor of epidemiology and health services research*

Faculty of Life and Health Sciences, University of Ulster, Belfast BT37 0QB

1 Elliott P, Briggs D, Morris D, de Hoogh C, Hurt C, Jensen T, et al. Risk of adverse birth outcomes in populations living near landfill sites. *BMJ* 2001;323:363-8.
2 Vrijheid M. Health effects of residence near hazardous waste landfill sites: a review of the epidemiological literature. *Environ Health Perspect* 2000;108:101-12.
3 Environmental Agency. *A practical guide to environmental risk assessment for waste management facilities*. London: EA, 2000. (Guidance note 25.)
4 Wilson J. *Environment and birth defects*. New York: Academic Press, 1973.

Improving endothelial vasomotor function

May reduce cardiovascular risk, but the current evidence is circumstantial

The vascular endothelium is a confluent, cellular monolayer that lines the entire vascular compartment at the interface between blood and the vessel wall. This "organ" possesses complex endocrine and paracrine functions and is intimately concerned in controlling vasomotor tone and preventing atherosclerosis and thrombosis.[1] Indeed, endothelial dysfunction plays a key part in the pathogenesis and progression of atherosclerosis.[2]

An important and relatively recently discovered endothelial product is nitric oxide, a simple, highly reactive gas previously known as endothelium-derived relaxing factor. Endothelial nitric oxide itself possesses potent antiatherogenic properties, inhibits platelet aggregation, and regulates vascular tone.[1] Bioavailable nitric oxide may be increased either by enhancing its production or by reducing its inactivation—for example, by reactive oxygen species, which are thought to damage the endothelium and promote atherosclerosis. Indirect measurement of bioavailable nitric oxide, through its vasodilating properties, is an extensively investigated surrogate of endothelial (vasomotor) function in clinical and experimental studies. In this context, endothelial vasomotor dysfunction occurs in the coronary arteries of patients with coronary atherosclerosis[3] and with standard risk factors for atherosclerosis,[4] and more recently it has been associated with the novel risk factors hyperhomocysteinaemia and low birth weight.[5]

Coronary endothelial vasomotor function may be assessed using quantitative angiography to measure vasodilatation induced by agonists (such as acetylcholine) or mechanical stimuli (increased flow) that stimulate the endothelium to produce nitric oxide; impaired function is associated with reduced dilatation. This assessment, although informative, is invasive and potentially hazardous and so not applicable to routine clinical practice. However, coronary endothelial vasomotor dysfunction has been shown to correlate closely with endothelial function measured in large peripheral arteries.[6] Measurement of endothelial function in accessible peripheral vessels, such as the brachial artery, is therefore a useful surrogate of coronary endothelial vasomotor function and can be measured by changes in forearm blood flow induced by nitric oxide releasing agonists (using venous plethysmography) or by flow mediated dilatation (using high resolution ultrasound).

Many studies have shown that endothelial vasomotor dysfunction is reversible with risk factor intervention (such as smoking cessation, physical exercise) and drugs (angiotensin converting enzyme inhibitors, statins, vitamin C, folic acid, fish oils, and spironolactone).[7–10] Until recently, however, we lacked clear evidence of a prognostic link between coronary endothelial vasomotor dysfunction and cardiovascular events. Two recent prospective studies have, for the first time, shown that coronary endothelial vasomotor dysfunction predicts cardiovascular events.[11 12]

Thus, if endothelial vasomotor dysfunction is associated with standard risk factors, can its measurement further improve risk stratification? This question has not been conclusively answered, though data from these prospective studies suggest that it may be more predictive of cardiovascular events than standard risk factors.[11] Furthermore, in people with mild coronary atheroma those with the greatest endothelial vasomotor dysfunction had a worse prognosis than those with mild dysfunction, there being no significant difference in risk factors or disease severity between the groups.[12] The observation that standard risk factor scoring in general practice in the United Kingdom will identify only 59% of men at risk of myocardial infarction or sudden death over a five year period is further evidence that standard risk factor detection will not reveal all those at risk of cardiac events.[13]

At present, clear prospective evidence for benefit, in terms of decreased cardiovascular events, after improving endothelial vasomotor function does not exist, although there is circumstantial evidence to support this link. Several large secondary prevention studies (4S, HOPE, RALES, GISSI Prevenzione study) have shown clear benefit in patients treated with different

BMJ 2001;323:352–3