COMMENTARY

Where the boys aren't: dioxin and the sex ratio

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Dioxins have the well-deserved reputation of being the most potent man-made biological agents and, along with their biological/chemical cousins, the coplanar polychlorinated biphenyl and polychlorinated dibenzofurans, they are ubiquitous in the environment, although usually at low concentrations. The low concentrations can become biologically magnified in the food chain as these lipophilic and hydrophobic substances get concentrated during their move from soil and sediment to fish or animal feed, to dairy and meat products, and eventually to the top of the food chain, human beings. Two Research Letters in today's *Lancet* show how contamination of the oceans, and of animal feed, can produce significant exposure of human beings to dioxins. Also in this issue of *The Lancet* is an article, by Paolo Mocarelli and colleagues, which provides intriguing and worrying results of how exposure to dioxins might affect people who consume dioxin-contaminated food.

Mocarelli and colleagues have been following up an extremely important cohort in Seveso, Italy, since 1976, when an explosion at a herbicide plant contaminated a wide area with dioxins. About 750 people in the cohort came from the most contaminated area and another 40 000 from two lesser-contaminated zones. They have been examined in several important studies on the effects of these hazardous environmental contaminants. Today's report is on possible reproductive effects.

For the study the marker of reproductive effect was the male-to-female ratio at birth. This sex ratio has been proposed as a sensitive marker of exposure to toxic chemicals in utero,[1] and earlier Seveso results[2] of a low male-to-female ratio at birth were considered suggestive evidence of an adverse reproductive effect.[1] Today's paper is a report of a more detailed examination of this issue—with, for example, more years of observation and sub-analyses by age strata. On such subanalysis reports significantly fewer male offspring (50 males *vs* 81 females) of fathers who were under 19 in 1976.

The results are provocative, although how dioxin reduces the number of sons is unclear. Mocarelli and colleagues refer to animal studies that suggest a mechanism in dioxin-exposed rat dams. Why exposure preferentially affects male embryos is not explained by Mocarelli and colleagues. Other investigators have proposed hormonal[3] or mutational[4] explanations, but these mechanisms may not apply to dioxin. A more parsimonious explanation follows from the fact that dioxin has been shown to be fetotoxic in animal studies.[5] It is a public-health maxim that males have shorter life-expectancies than females at every age from conception onward. On this basis, if in-utero exposures are toxic to both sexes, one might expect greater fetal loss in males. Whatever the mechanism, the Seveso finding is of public-health interest since it was seen at exposure levels that are lower than those associated with many of the other effects of dioxin. Of ancillary, but especial importance, is the indication in today's report that residents of Seveso were exposed to significant levels of dioxin even before the explosion in July 1976, a finding that could have repercussions for other industrial plants.

The study, by H Kiviranta and colleagues, of dioxin exposure in fish in Finland is also of public-health interest because it suggests that dioxin and dioxin-like compounds bioconcentrate in the aquatic food chain in ways that might allow identification of the species of fish that was initially contaminated. Somewhat surprisingly, the Finnish researchers found that different congeners of dioxin and dioxin-like compounds in biological samples were associated with different fish species eaten. If taken further back down the food chain, this finding raises the possibility of identifying the actual source of the contamination, and points to the need for more sampling of fish species to inform authorities that advise on public consumption. These results underscore the importance of recognising exposures in certain special populations, such as fishermen.

Fish are not the only, or even the main, source of dioxin exposure in the general population. Dairy and meat products are the main sources of exposure for most Europeans (see, for example, ref 6 for data from The Netherlands). A public-health furore arose in many European countries[7] when dioxin-contaminated feed led to deaths of chickens in Belgium. Dioxin contamination was suspected because the dying chickens exhibited a type of oedema characteristic of such exposure. The slow reaction by the government agency responsible for protecting the food supply had major political ramifications. This experience reinforces lessons learned by some public-health agencies in the USA.[8] The folly of attempting to withhold information or acting as departments of public reassurance can result in a serious erosion of public trust.

Prevention of such episodes of contamination depends upon effective and efficient means of detecting incipient contamination of food supply. The adoption of an action level, with systematic sampling for dioxin-like chemicals in animal feed, would be an important step. An action level

of 2 pg/g feed for hens and pigs has been suggested by an expert group from EU countries, and Austria has adopted this recommendation for feed for broiler chickens, the focus of the recent Belgian episode, and for pigs. The report by M Neuberger and colleagues in today's *Lancet* shows that adoption of this action level would have detected and prevented the Belgian episode.

These recent examples of dioxin exposure in the food chain in Europe, and the provocative finding of the altered sex ratio, especially among offspring of people exposed to dioxin when they were young, highlight the interest in the health effects of these and related compounds. An enormous amount of information has been compiled on the range and mechanisms of adverse effects of dioxin and dioxin-like compounds in the past two decades. The US Environmental Protection Agency (EPA) undertook a reassessment of the health effects of dioxin in 1991, in a fairly open process that was supposed to take a year and a half. Although an eight-volume draft reassessment, which included a thorough review of human and animal data, was released in 1994, the final draft has not been published officially. An executive summary was leaked last week to the *Washington Post* and received wide coverage. The latest EPA draft has not yet gone through final peer review, which is expected to start next month. In the interim, the International Agency for Research on Cancer has re-classified tetrachloro-dibenzodioxin (TCDD) as a group I (established human) carcinogen,[9] and authoritative reviews of the health effects of exposure to herbicides used in Vietnam have been published.[10,11] Additional studies of the Vietnamese population have been proposed, to define the extent of the continuing health effects in those exposed to the dioxin contaminants of Agent Orange. The amount that has been learned, at levels ranging from intracellular, to interspecies, to intergovernmental, makes dioxin a chemical symbolic of the full impact of the chemical age on health.

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Youth and hormone receptors in breast cancer: good or bad news first?

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Clinicians have long suspected that young women with breast cancer do badly. They present with larger primary tumours, greater involvement of axillary lymph nodes and higher histological grade—factors associated with worse prognosis. The controversies have been whether youth itself conferred an additional penalty once account was taken of these factors and, if so, how this might be affected by treatment.

Today's report from the International Breast Cancer Study Group provides data on 3700 premenopausal or perimenopausal women with early breast cancer who received adjuvant chemotherapy in successive randomised trials. None had adjuvant tamoxifen and fewer than 5% had adjuvant ovarian ablation. The 314 women aged under 35 did substantially worse than the 3386 women aged 35 or over (10-year disease-free survivals of 35% versus 47%, $p<0{\cdot}001$; 10-year survivals of 49% versus 62%, $p<0{\cdot}001$).

The striking unexpected finding is that the adverse effect of youth seems confined to women with oestrogen-receptor-positive (ER+) tumours. Women under 35 with ER+ tumours did very badly (10-year disease-free survival of 25%, overall survival of 39%), whereas women under 35 with ER-tumours did as well as women 35 and over, among whom ER status had little impact on outcome (10-year disease-free survivals of about 46%, overall survival of about 60%; p values for interactions: 0·002 and 0·01, respectively). These differences persisted after adjustment for tumour size, grade, and lymph-node involvement and were most evident in women who continued to menstruate after completing chemotherapy.

This counterintuitive interaction between age and ER status could be due to bias or chance, but rigorous methods and low p-values suggest otherwise. The alternative explanation is that lengthy exposure to premenopausal concentrations of sex hormones is harmful to young women with ER+ tumours. This explanation would account for the apparent conflict with the prevailing view (and data) that women with ER+ tumours do better.

Because the incidence of breast cancer increases steeply with age, most affected women are postmenopausal or soon become so. Thus, the prognosis of the majority with ER+ tumours reflects the absence of premenopausal ovarian function. In contrast, only a small proportion of women with ER+ tumours develop them long enough before menopause to reflect the effects of lengthy exposure to premenopausal sex-hormone concentrations. Detection of such an effect on prognosis requires specifically looking for, recognising, and understanding interactions. This particular interaction is crucial because it suggests use of specific treatments of proven benefit—tamoxifen and ovarian ablation.

A recent population-based study of over 10 000 women aged under 50 with early breast cancer corroborates the finding of worse outcomes for younger women.[1] In that study the risk of death in women under 35 was 1·5 times that of women aged 35 to 50. The striking finding there was that the increased risk of death was greatest in women with low-risk tumours who did not receive adjuvant chemotherapy. The differences in outcome remained after adjustment for differences in tumour size, grade, and