CAN STUDIES BY A SINGLE INVESTIGATOR OVERRIDE COLLECTIVE EVIDENCE? THE CASE OF DIOXIN

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Introduction

With very few exceptions, it is a laborious process to establish or exclude confidently whether a factor causes human cancer. The debate concerning dioxin illustrates the complexity of this process, but it has also some unusual characteristics. Most notably, the epidemiologic evidence that dioxin may increase cancer risk in humans comes largely from one investigator. Over a period of two decades, this investigator has published a series of epidemiologic studies on different cancers. And all of them suggested positive associations with dioxin and/or other related environmental pollutants. In the evaluation of most other chemicals or groups of chemicals the pattern of results has been different, involving several investigators in each side of a controversial issue.

Methods and Materials

A detailed evaluation of the set of studies on dioxin by this investigator will follow the structure usually applied in epidemiology. Hence, I will discuss specifically how bias, confounding and chance might have influenced results and interpretations.

Bias can arise through numerous mechanisms. The case-control design, consistently used by this investigator, is particularly liable to several of them. Subtle bias of uncertain direction can arise if cases and controls are not derived from exactly the same population (study base). This problem becomes relevant for example if some participants are deceased at the time of investigation. Information bias is another potentially serious methodologic problem. In general, it is likely that cancer patients (cases) or their relatives (proxy responders) are more motivated to provide a detailed account of work history and occupational exposures than healthy subjects (or their relatives). Obviously, this would entail exaggeration of risk estimates.

In the context of dioxin, confounding is an important concern, notably because many subjects exposed to dioxin are exposed also to other potentially carcinogenic compounds. To distinguish these correlated exposures from each other may be difficult. Indeed, the subjects themselves (let alone their relatives) may not know or not remember which mixture of compounds they were exposed to many years or decades earlier in life. Confounding can also arise because subjects whose work history indicated exposure to dioxin and related compounds may also have life style characteristics (such as smoking habits) that are etiologically relevant for several forms of cancer.

The play of chance is often a concern in studies of dioxin and cancer. First, even in large studies the number of exposed individuals is small. Hence, the precision of most risk estimates is low as

reflected by wide confidence intervals. Second, any statistically significant elevation in risk is likely the result of a multiple testing process. Hence, the de facto level of significance may be less impressive that the stated p-value.

In situations of uncertainty, a clear dose response trend may provide convincing evidence that in an association does indeed reflect a causal relationship. In studies of dioxin, however, such evidence is largely lacking because the number of exposed individuals is too small for a meaningful evaluation of dose trend relationships. Or because the exposure was measured too crudely for an informative classification of dose.

Results and Discussion

There can be little doubt that this particular investigator has done a dedicated job over a long period of time. Moreover, the respective studies have all been carried out in Sweden, a country where prerequisites for high quality epidemiologic investigations are excellent. Hence, it would be cavalier to dismiss these studies without careful scrutiny. Such scrutiny reveals, however, numerous potential sources of bias in the Swedish studies, all of them carried out with a similar design. It is a possibility – but also a speculation that cannot be empirically proven – that systematically exaggerated risk estimates are the net effect of imperfect methodology.

Studies with a higher level of ambition would be needed to demonstrate convincingly whether dioxin is associated or not with any specific cancer site or type in humans. Ideally such studies should be large, include only incident cases of cancer and allow careful and validated assessment of exposure to dioxin and to confounding factors.

References (sample)

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