Letter to the Editor

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Cadmium from zinc smelter emission and variation in cancer incidence: the hierarchy of evidence

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The conclusion in the recent report of Verhoeven *et al.* (2011) on the incidence of cancer in relation to cadmium (Cd) emission of zinc smelters in the Belgian Noorderkempen remains far from convincing and is at variance with our results (Nawrot *et al.*, 2006). We showed that the risk of lung cancer significantly correlated with indicators of environmental Cd exposure (soil Cd, residence in a high-exposure area), and more importantly, that all-cancer, lung cancer risk, and mortality were significantly dose-related with 24 h urinary excretion of Cd (Nawrot *et al.*, 2006, 2008), a good surrogate biomarker of internal Cd dose reflecting an individual's lifetime-integrated Cd exposure. The four-fold increased risk of lung cancer found in the high-exposure area (Nawrot *et al.*, 2006) could by no means be extrapolated to the entire territory of the municipalities in Verhoeven's analysis, as our prospective cohort study included habitants living within 3 km of the zinc/Cd smelters.

In 2003, two co-authors of the Verhoeven article co-authored a first paper on cancer incidence in the Belgian province of Limburg (Buntinx *et al.*, 2003) and stated without any reference to zinc smelters that 'In summary, our results support the hypothesis of an absence of geographical differences between municipalities with respect to incidence of cancer, including the most frequent cancer sites separately'. Because the available data were municipality related, Buntinx *et al.* (2003) recognized vulnerability to ecological bias and rightly concluded that 'Final conclusions about possible explanations can only be based on epidemiological research using a retrospective cohort or case-control design with the individual as the unit of analysis'. This sound scientific awareness of the pitfalls associated with the interpretation of ecological analyses has been overridden by Verhoeven *et al.* (2011) when concluding that 'the long term emission of cadmium by zinc smelters in the Kempen area did not seem to lead to an increase in the incidence of all cancers, and lung cancer'. Although the Verhoeven *et al.* (2011) report seems to confirm largely the results of Buntinx *et al.* (2003) for the Belgian Kempen area, it manifestly deviates from the authors' statement that 'our study was designed [……] not to study the etiologic relation between an exposure and the risk of cancer'. Obviously, the paper, not the least the title, does convey an etiologic link between Cd emission of zinc smelters and cancer incidence. The negative outcome is driven by analyses at the municipality level on the basis of the Kulldorff (1997) spatial scan statistic. It is known that the use of circular regions lacks power for cluster detection when there are multiple very small clusters at very different locations (Kulldorff *et al.*, 1998), an alternative that is exactly represented by the geographical distribution of the lung cancer incidence recorded by Nawrot *et al.* (2006) within the perimeter of the five small residential areas in the vicinity (< 3 km) of zinc/Cd smelters. The statistics used by Verhoeven *et al.* (2011) were inadequate to detect the clusters of all-cancer and lung cancer that Nawrot *et al.* (2006) were able to evidence on a geographical scale level much smaller than the municipality level. Hence, the conclusion of the Verhoeven *et al.* (2011) study, that cancer incidence variation in the Kempen area seems to be unrelated to Cd emission of zinc smelters, is not valid and incorrect. Not only does it illustrate the risk of fallacy prone to the interpretation of results generated from population studies using aggregate-level data but also it shows that deduction of individual-level effects from group-level data on the basis of such studies often results in ecologic biases (Järup and Best, 2003).

In contrast to our prospective data in individual participants, Verhoeven and colleagues did not quantify individual Cd exposure, but focused the cancer cluster scans on municipalities located close to zinc smelters, a most unspecific surrogate group-level variable to characterize hazardous exposure. In his paper *The environment and disease: association or causation?*, Hill (1965) postulated six key criteria as guidelines for causality: the timeline, the strength of the association, the presence of a dose–effect relation, the consistency of the findings, the specificity, and biological plausibility of the association. In contrast with Verhoeven *et al.* (2011), our finding of a Cd dose-related increase of lung cancer risk complies with all Hill's criteria of causation (Nawrot *et al.*, 2007).

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Furthermore, in their discussion, Verhoeven *et al.* (2011) qualified our prospective cohort analysis, the gold standard in observational epidemiology, as a case–control study, a lower ranked study design in the hierarchy of gathering observational evidence. Moreover, the authors applied smoothing techniques at the level of municipality, including municipalities with and without zinc smelters on their territory. The Verhoeven *et al.* (2011) results, on the basis of aggregate-level data, are likely to suffer from two flaws involving incorrect presentation of cancer risk including background risk. First, they considered only areas close to the primary zinc smelters of Lommel, Overpelt, and Budel, but neglected to take into account other municipalities that had on their territories polluting activities of at least two other zinc smelters (Balen in the Noorderkempen, Dilsen-Stokkem in East-Limburg) and an arsenic refinery (Reppel) that were mistakenly considered as control municipalities. The soil in all these areas is heavily polluted by toxic metals including Cd (Bosmans and Paenhuys, 1980). Second, they included municipalities in which large proportions of the inhabitants were occupationally active coal miners with a known high risk of pneumoconiosis and associated cancers (Cohen and Velho, 2002). In our prospective analyses (Nawrot *et al.*, 2006; Nawrot *et al.*, 2008), all coal mine workers were excluded to obtain a correct background cancer risk. These deficiencies are likely to compromise the outcome of the smoothing and spatial scan statistics Verhoeven *et al.* (2011) applied to study cancer incidence in the Belgian part of the Kempen area.

In conclusion, Verhoeven's study ranks low in the hierarchy of epidemiological evidence and risks distracting attention from the sanitation and preventive measures that should be implemented in the heavily polluted zinc smelter areas of the Belgian Noorderkempen.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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