## APPENDIX 9. Comber 2015 review

### Comber 2011 Ireland osteosarcoma-F study review for NTP cancer review

Chris Neurath  November 12, 2015, revised November 29, 2015

Comber's [2011] ecological study examining osteosarcoma rates in fluoridated and unfluoridated locations in the Republic of Ireland (RoI) and Northern Ireland (NI) is limited in its ability to detect any association.

Comber had a small sample size, especially for an ecological study. Only 77 osteosarcoma cases occurred in males <25 years old. Compare this to Blakey's sample of about 1000 such cases. Comber's small sample size limits the power of the study to find an effect.

**1. Lack of control for potential confounders.** Comber did not control for potential confounders, such as socio-economic status (SES) or rural versus urban. All of his fluoridated cases were from rural areas of RoI and none from urban areas, so the potential for confounding on rural versus urban is great. Similarly, SES is often associated with rural residence. SES and rural versus urban have been found to be risk factors for osteosarcoma in Great Britain [McNally 2012]. Strong associations between SES and total F exposure have been found in other studies [Fergusson 1986].

**2. Exposure uncertainties led to low power to detect differences in osteosarcoma rates between fluoridated and unfluoridated areas.** Although it uses fairly small area data (electoral divisions) with average population of 1100, the fluoridation status of each electoral division in RoI was determined solely on the basis of its population density. The assumption being that rural areas were not fluoridated and urban areas were. This likely resulted in some exposure misclassification, although the degree was not determined. For NI, exposure status could be reliably assigned because there is no fluoridation in NI. But since all comparisons of osteosarcoma rates relied on the fluoridated parts of RoI, the consequence is that their exposure misclassification would likely bias results toward the null, making it more difficult to detect any real effects.

Another source of exposure uncertainty is due to population mobility. Fluoridation status was assigned based on residence at the time of diagnosis of osteosarcoma. This can not account for previous residences in places with different fluoridation status.

This will lead to non-differential misclassification of exposure, leading to bias toward the null, as explained by Houghton [2003a, 2003b]. Long [1991] reported that in Ireland (RoI) the percentage of people who moved during one year was 6%. Although no data was available for mobility over a 5 year or longer period, Long found 5-year rates for countries were typically 2.5 times greater than the 1-year rate, so that Ireland would have a

predicted 5-year mobility of 15%. For 10 to 20-year periods the mobility would be much greater, so that it is likely that 30% or more of Comber's subjects would have had a different residence than the one at diagnosis. Long [1992] found that mobility was especially high in the childhood and teenage years, the time period most relevant to risk of osteosarcoma. In addition, Long [1992] found that moves to a different county in RoI represented a substantial portion of moves. Moves of this distance have the most potential to result in a change in fluoridation status.

The implication of these rates of mobility to Comber's study is that 30% or more of his subjects may have had their fluoride exposure misclassified. Such rates of misclassification would bias his results strongly toward the null. This same problem exists for all existing ecological F-cancer studies, all of which assign fluoride exposure status from a single time point.

No attempts to account for fluoride exposures other than water fluoridation were made. For Ireland, which has amongst the highest tea consumption per person in the world, this is a serious limitation. Studies have shown that children in Great Britain, another nation with very high tea consumption, consumed enough fluoride from tea that there was little difference in total F intake between areas with and without water fluoridation [Rao 1984 Cook 1969a, 1969b, 1970, 1976]. For adults in Great Britain a similar finding was made based on urine F levels, which are a good biomarker of total F intake [Mansfield 2010]. Comber states that 1/3$^{rd}$ or more of total F intake may be from sources other than fluoridated water, like tea. However, his reference is a WHO report which contains no information on total F intake from countries with very high tea intake such as Ireland. Tea may actually contribute much more than 1/3$^{rd}$ of total F intake in Ireland.

Another source of potentially high F intake is F supplements. These are typically only prescribed for children who live in unfluoridated areas. No information could be found on the rates of F supplement usage in Ireland, although supplements are recommended for children in unfluoridated areas of Ireland. To the extent supplements are used in unfluoridated areas of Ireland, Comber's results will be biased toward the null.

With regards to the relative contribution of drinking water F to total F intake Comber states:

> "While fluoride in drinking water probably represents the greater part of the total dietary intake of fluoride, at least one third of fluoride intake is estimated to come from other sources. Consumption of high-fluoride foods such as tea and certain fish may increase intake significantly; toothpaste is another important source of fluoride."

However, Comber offers no supporting references for the claim that drinking water provides the majority of total dietary F in Ireland. Blakey [2014] made a similar claim in her ecological study of F and osteosarcoma in Great Britain, and provided a singl reference. That reference was a review that only referenced studies in the USA. The per capita consumption of tea in the USA is 1/10$^{th}$ that in Ireland, so F from tea in Ireland may represent much more than 1/3$^{rd}$ of total F intake.

Based on these misclassifications and limitations of total F intake in Comber's study, the power to detect an effect was likely much less than that stated by Comber.

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