APPENDIX 8-A. Blakey/McNally 2014 review

Review of Blakey 2014 fluoride---osteosarcoma ecological study Great Britain.

Chris Neurath, December 11, 2015

The Blakey et al. [2014] study, which found no association between drinking water fluoride (F) level and risk of bone cancers, has several important limitations. It is ecological and despite it's use of small area information on drinking water F, suffers from problems in exposure estimates. There are several sources of exposure misclassification, some non---differential so they will lead to bias toward the null or "no effect". Others are differential and may cause bias away from a positive association between F and osteosarcoma, potentially even to the extent of a spurious finding that F protects against osteosarcoma. Each limitation will be described individually.

LIMITATION OVERVIEW:

1. Blakey had no information on F exposures other than the drinking water F concentration.

2. Blakey's study used no age history of exposure.

3. Exposure misclassification. Blakey used the water F level of each small geographic area in 2004---2006 to assign F exposures to each subject, even though most of the relevant exposure years would have been between 1930---2000. Many of the areas that were fluoridated by 2004---2006 were not yet fluoridated for much of the time period 1930---2000.

4. Potential for confounding is increased in Blakey's study because in the UK, fluoridated water is not randomly distributed geographically but is mostly in a single area.

5. Apparent misclassification of bone cancer subtypes in the West Midlands Cancer Registry, which encompassed most of the fluoridated population of Great Britain. Alternately, alteration of bone cancer numbers following reorganization of West Midlands Cancer Registry.

6. Did not control for radon exposure, which has been found to be a risk factor for childhood osteosarcoma in a recent study.

1. Blakey had no information on F exposures other than the drinking water F concentration. She did not have information on amount of water consumed, on any dietary sources, and on any dental F sources such as swallowed fluoridated toothpaste, dental office F

treatments, and F supplements. For children, swallowed toothpaste is a major source of fluoride. This was confirmed recently in a carefully conducted study of fluoride exposure among British children. [Zohoori 2012]. Further, in the UK, tea (*Camellia sinensis*) is a major source of dietary F, much more so than in North America, where most fluoride---osteosarcoma studies have taken place. Per capita tea consumption in the UK is about 10 times greater than in the USA [Wikipedia 2015 FAO data on per tea consumption by country]. For the time period when most of Blakey's subjects would have been children (1960---1980) studies of childhood tea consumption show that many UK children may have consumed more F from tea than from fluoridated water [Rao 1984; Cook 1969a, 1969b, 1970, 1976]. In one study from 1970, it was found that of 662 children age 5---16 in 10 different schools the average F intake from tea was 1.26 mg/day, a high amount. 93% of children drank tea, with an average of 2.4 cups per day, even for the youngest [Cook 1970]. Another study in 1984 found that from age <1 – 8 the average intake of F from tea was 0.4 mg/day, which would still be a relatively high proportion of total F intake, even in a fluoridated area. A recent UK national survey measured urine F levels, which are a good biomarker of total F intake, and found many people had levels higher than could be explained by F intake from drinking water [Mansfield 2010]. An older study using bone F as a biomarker for long time total F intake compared Great Britain to the USA, taking into account tea consumption. It concluded that tea consumption in non---fluoridated areas of Great Britain led to similar elevated bone F levels as water fluoridated at 1 ppm in the USA which has very low tea consumption compared to Great Britain [Jackson 1958].

Blakey had no information on F supplement usage. In countries with water fluoridation, it is common for dentists, pediatricians, and public health programs to recommend F supplements to children in the non---fluoridated areas, but not in fluoridated areas. Great Britain has recommended such supplements for many years [Banting 1999]. A study in New Zealand found that even very low dose F supplements could lead to higher total F exposure than from fluoridated water [Chowdhury 1996]. To the extent F supplements were used in non---fluoridated parts of Britain, their use would bias Blakey's results away from a positive effect. The only information found on F supplement use in the UK was from a 2004 paper which says, "the use of supplements is not extensive" [Whelton 2004]. However, the relevant time period for the Blakey study extends back to 1930, when the oldest subjects would have been born. Most subjects would have reached the peak age for osteosarcoma by about 1990. So, it is F supplement use before 1990 that is relevant. Great Britain recommended F supplements during this time [Banting 1999].

A uniquely diagnostic biomarker of total F exposure during childhood is dental fluorosis. Numerous studies have found a strong correlation between total F exposure and prevalence and severity of dental fluorosis [Ziegelbecker 1981, Dean 1937]. To assess the total childhood exposure of Blakey's subjects to F, examination of existing UK studies on dental fluorosis are illuminating. Holloway [1997] reviewed the prevalence of dental fluorosis in the UK, over time, and in relationship to whether drinking water was fluoridated or not. He found very little difference in enamel defect prevalence (about half of which is dental fluorosis) between fluoridated and unfluoridated areas, especially before 1980. Based on a number of studies, he reported:

> "… there is little evidence to suggest that in the UK, up to approximately 1980, a fluoride concentration in the water supply of 1 mg/l had any effect on the overall prevalence of enamel defects."

> "It would seem from this varied collection of reports (Table 6) that the prevalence of developmental defects of enamel in communities receiving optimally fluoridated water is now slightly higher than that in communities receiving fluoride---deficient water and that this may not have been the case some 20 years ago."

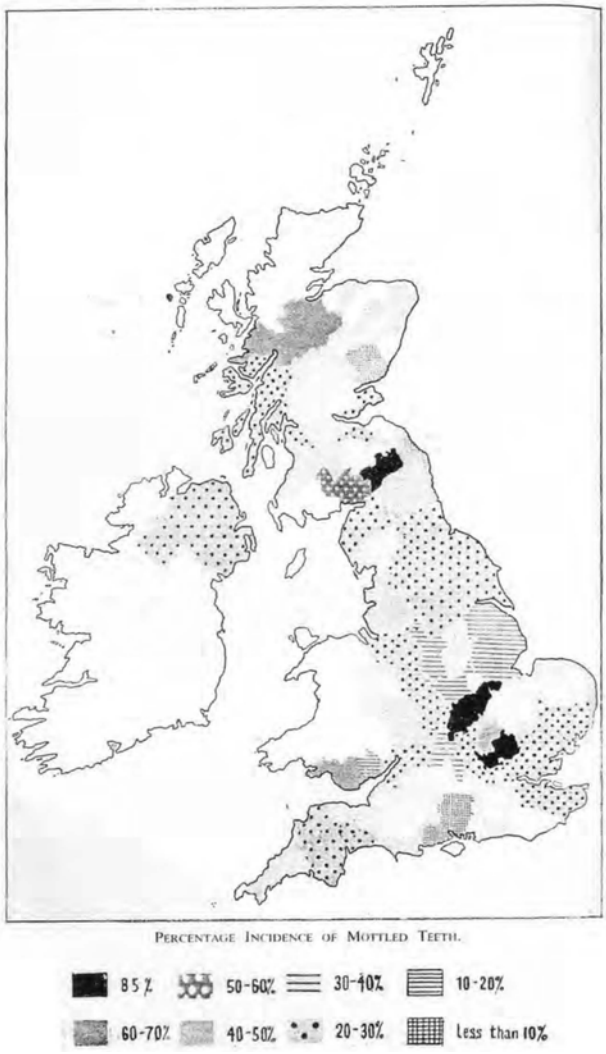
Holloway's pre---1980 data, when averaged, in fact show slightly higher enamel defect prevalence in low water fluoride areas compared to high fluoride areas [Holloway 1997, Table 5]. For many of Blakey's subjects, pre---1980 total F exposures are the most relevant to subsequent risk of osteosarcoma. Dental fluorosis prevalence data suggests there was virtually no difference between fluoridated and unfluoridated areas during this period.

It is also important to note that the overall rate of dental fluorosis in unfluoridated areas of the UK from the 1950s to the 1980s was substantially higher than in the US, even though the UK had substantially lower nationwide fluoridation rates [Holloway 1997, Heller 1997]. This implies that sources other than drinking water supplied most of the fluoride exposure in the UK.

The most likely explanation for this finding and the finding that pre---1980 fluorosis rates in the UK were the same in fluoridated and unfluoridated areas is high childhood tea consumption [Rao 1984; Cook 1969a, 1969b, 1970, 1976]. Other possibilities are use of F supplements, F toothpaste, F mouthwash, F dental treatments, or even lingering F air pollution from industries and domestic coal burning. However, most of these additional F sources may have been similar in the UK and USA, which leaves tea consumption as the most likely explanation.

A single UK---wide study of human dental fluorosis prevalence rate, by county, was identified [Spira 1942]. It is from the 1940s, before any water fluoridation program had yet been implemented. The survey was of British Army recruits who came from across the UK. A map of the results shows both very high rates of dental fluorosis at that time (much higher than can be explained by F in drinking water), and some distinctive geographic patterns. Figure 1 shows the map.

Figure 1. Map of dental fluorosis prevalence, a biomarker of total F exposure, in the 1940s, by county [from Spira 1942].



The London area has 85% prevalence of dental fluorosis, as do two other areas. Most counties had greater than 10% prevalence, with many having substantially higher prevalence. These high fluorosis rates across the UK strongly suggest that there was an F source that was much greater than what could be had from F in drinking water. Childhood tea consumption seems the most likely explanation for the generally high rates, but does not explain the wide county---to---county variation. F air pollution might explain the variation. At the time, industrial F air emissions were unregulated, and domestic coal burning, such as in London, was also a known source of high F air concentrations. Additional evidence shows that high levels of airbone F affected large areas in the UK. A study from the 1950s showed that fluorosis in livestock was strongly associated with industrial sources of F air pollution, as seen in the Figure 2 map of Great Britain [Weinstein 2004]. This study only looked at livestock fluorosis, not human, which may explain why London was not identified as an area of high prevalence in this study yet was identified in Spira's [1942] survey.

Figure 2. Map of areas with high F exposure due to industrial air pollution [from Weinstein 2004].

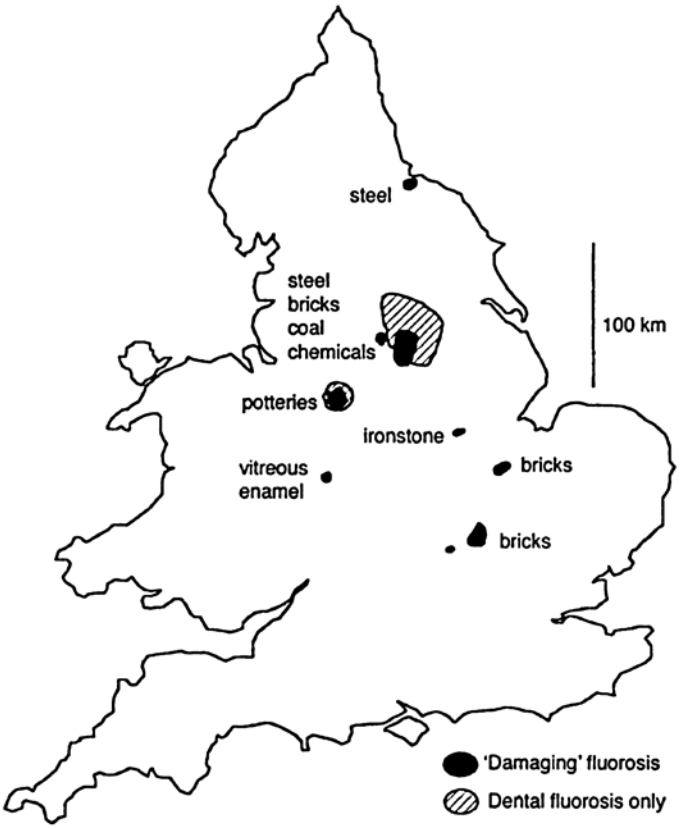


Fig. 3.3. Areas of England and Wales where industrial fluorosis was found in the 1950s, and the main sources of fluorides. (Redrawn and modified from Burns, K.N., Allcroft, R. (1964) Fluorosis in cattle in England Wales. 1. Occurrence and Effects in Industrial Areas of England and Wales 1954–57. Ministry of Agriculture, Fisheries and Food, Animal Disease Surveys Report No. 2, Part 1. Her Majesty's Stationery Office, London, according to licence number C02W0002815.)

In summary, drinking water F represents a minority of the total F exposure for many people in the UK, especially during the most relevant time period for the Blakey subjects of 1950---2000. Dental fluorosis evidence suggests that before about 1980 there was almost no difference in total F intake in fluoridated areas compared to unfluoridated. This may explain Blakey's finding of no association between drinking water F and risk of osteosarcoma. The UK is not a good area to look for health associations with fluoridated water, since tea and other sources may contribute more total F than fluoridated water. Blakey relies on a single reference to argue that water fluoridation would represent at least half of total F intake. But that reference is a review of other studies, all of which were done in the USA where tea contributes very little to total F [Harrison 2005, Hamilton 1992].

2. Blakey's study used no age history of exposure. All exposures were based on residence location at time of diagnosis/referent, with no account of residential mobility. 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 Great Britain the percentage of people who moved during one year was 10%. 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 Great Britain would have a 5---year mobility of 25%. For 10 or 20---year periods the mobility would be much greater, so that it is likely that 50% or more of Blakey's subjects would have had a different residence than the one at diagnosis/referent. 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 Great Britain 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 Blakey's study is that as many as 50% or more of her subjects may have had their fluoride exposure misclassified. Such rates of misclassification would bias her results strongly toward the null. This same problem exists for all ecological F---cancer studies, all of which assign fluoride exposure status from a single time point.

In contrast, two studies had complete histories of fluoride exposure. Gelberg [1994, 1995] and Bassin's [2001, 2006] case---control studies, which looked at complete residential history, found that the mean number of residences was 3 by the age of diagnosis. Importantly, these studies restricted age to those with diagnosis below age 25 and age 20 respectively. Those cases who are 20 and older likely have an even higher chance of not living in the same location as they grew up The latency of osteosarcoma is probably at least 3 years, and more likely 5 to 10 years [Chmelevsky 1988], so past exposure is much more relevant than exposure at time of diagnosis. It is noteworthy that all the studies which have found a positive association between F exposure and osteosarcoma have restricted the age to less than 20 [Hoover 1991, Cohn 1992, Bassin 2006].

Also in regard to timing of exposure, Blakey had no information on age---specific exposures. This is a major difference between Blakey's study and Bassin's, which uniquely looked at age of exposure by single years. Bassin found that there was a time window of susceptibility from exposure between ages 5 and 10, for developing osteosarcoma about 5 to 10 years later. Blakey misinterpreted Bassin's study by suggesting that Bassin's results were based on the very small proportion of subjects who were *diagnosed* between age 6 and 8, when in fact Bassin's results were based on her full sample, which had a sharp peak of diagnosis around age 15. This is close to the peak age of diagnosis in the USA and UK which indicates Bassin's sample selection was not biased with respect to age of diagnosis.

Blakey also implies that Bassin's smaller total sample size than Blakey's suggests a lower power and therefore undermines the validity of Bassin's finding. It is unclear how Blakey can claim her ecological study is more valid than Bassin's case---control study because its sample size is larger. The different study designs are "apples and oranges". It could as well be said that despite Blakey having a much larger sample size, Blakey's less precise and possibly biased exposure information and less sensitive study design prevented Blakey from detecting the effect which Bassin was able to find. Further, Bassin's study has one of the largest sample sizes of all case---control studies on fluoride and osteosarcoma for the age range of greatest interest: age 0 to 20. [McGuire 1991, Gelberg 1995, Bassin 2006, Kim 2011].

Blakey has a fundamental misunderstanding of Bassin's study, which apparently led to Blakey's statement that Bassin's study was very low powered. This misunderstanding was shared by the NRC 2006 review and many other commentators on Bassin's study. The misunderstanding is based on confusing age of exposure with age of diagnosis.

Here is what Blakey says:

> "In a recent case---control study, Bassin and colleagues analyzed 103 cases (60 males, 43 females) aged under 20 years and found increased osteosarcoma risk with fluoride in drinking water for males only, with a peak in the age---group 6–8 years.[47] However, the number of cases within this age---group would have been extremely small.[49,50]"

While it is true that the number of cases *diagnosed* with osteosarcoma in the 6---8 age group is a small proportion of the total cases, Bassin's study actually was looking at the risk of osteosarcoma diagnoses from *exposures* at ages 6---8. Typically, diagnoses did not occur for another 5 to 10 years, which could be considered the latency period. By age 11---19, when the diagnoses occurred, those cases constituted a large majority of the cases, not an "extremely small" number. Furthermore whatever the sample size may have been, the results were highly statistically significant, so there was sufficient power to demonstrate an effect. Blakey's criticism that the study is underpowered is not only unwarranted but refuted by the study's findings.

This misunderstanding means people have not grasped one of the most important strengths of Bassin's study, a strength that has not been duplicated in any study before or since. Bassin's study is more powerful precisely because it looked at risk by age---specific exposures. This is discussed more fully in our reviews of Bassin's and Kim's [2011] studies. [Appendix 6---A.]

3. Exposure misclassification. Blakey used the water F level of each small geographic area in 2004---2006 to assign F exposures to each subject, even though most of the relevant exposure years would have been between 1930---2000. Many of the areas that were fluoridated by 2004---2006 were not yet fluoridated for much of the time period 1930---2000. Blakey acknowledges this is a limitation of her study:

> "Lack of availability and inconsistency of individual sampling data across the whole of GB during the study period (only 2004–06 data were used) meant an assumption was made of no change in fluoride levels within the study time---frame."

An examination of the history of fluoridation schemes in Britain reveals, in fact, that about 33% of the population with fluoridated water in 2004---2006 did not have fluoridated water between 1950---2000, the years likely to be most relevant to osteosarcoma etiology [see below for calculations; British Fluoridation Society 2012]. This means about 33% of the relevant person--- years of exposure were misclassified as "exposed" when in fact they were "unexposed". This would bias Blakey's results away from an effect of fluoride.

Also important, is that the latency period for osteosarcoma is likely to be 5---10 years for children and teens. Blakey did not attempt to lag exposure for such a latency period. A person diagnosed with osteosarcoma in 1980 (the earliest year of data) when they were age 15 (a peak age) would ideally have their exposure determined by the water fluoride level at least 5 years earlier, in 1975.

The time history of fluoridation in Great Britain is quite relevant to Blakey's analysis, and it appears that by only using 2004---2006 fluoride levels, Blakey may have misclassified a significant portion of her subjects. The British Fluoridation Society (2012) gives information on the time history of fluoridation in Great Britain. Substantial increases in fluoridated populations occurred in the 1980s in the West Midlands.

Blakey's birth cohort analyses do not really address this issue, given the specific dates mentioned above. Furthermore, Blakey found the Relative Risk (RR) to increase with each subsequent birth cohort, exactly as would be expected if such a misclassification was occurring. The more recent the birth cohort, the less the misclassification, the higher the Relative Risk.

Calculations to determine the extent of misclassification of fluoride exposure:

From the British Fluoridation Society's "One in a Million" report [British Fluoridation Society 2012], in 2012:

> 5.8 million people in Great Britain had artificially fluoridated water
> 0.3 million have naturally fluoridated water
>
> Combined this represents 10% of the population of Great Britain.

The report further breaks this down by location and the start times of fluoridation schemes in each location, as shown in Table 1.

Table 1. Time history of fluoridation in English cities

#	Location	Population	Mean Start	First Start	End Start	Notes
1.	Cumbria	120,000,	1970	1969	1971	suspended 2006
2.	Cheshire	137,000	1968	1968		
3.	Tyneside	643,000	1968	1968		
4.	Northumberland	101,000	1968	1968		
5.	Durham	85,000	1968	1968		
6.	Humberside	136,000	1969	1968	1969	
7.	Lincolnshire	250,000	1969	1968	1969?	
8.	Nottinghamshire	287,000	1975	mid---1970's		
9.	Derbyshire	43,000	1980	1972	1987	start dates from: https://www.whatdotheyknow.com/request/44073/response/112189/attach/6/Fluoridation%20paperjan09.doc
10.	West Midlands	*below:*				
10a.	Birmingham	1,000,000	1964	1964		mid---1980s Sutton Coldfield added (unknown population)
10b.	Solihull	200,000	1964	1964		added in mid---1980s the towns S and E of Solihull including Knowle, Dorridge, Meriden, and Balsall Common
10c.	Coventry	300,000	1985	1981	1989	
10d.	Sandwell	300,000	1986	1986		
10e.	Dudley	305,000	1987	1986	1988	
10f.	Walsall	253,000	1986	1985	1987	
10g.	Wolverhampton	236,000	1986	1986		
11.	Staffordshire	497,000	1987	1986	1988	(One town has natural F: Uttoexeter 13,000)
12.	Shropshire	22,000	1987	mid to late 1980s		
13.	Warwickshire	~500,000	1976	1964	1987	
14.	Worcestershire	253,000	1981	1970	1991	
15.	Bedfordshire	198,000	1973	(not stated)		

NOTE: An Excel worksheet with this data and calculations of percent misclassified is available in Appendix 8---B.

We calculated the percentage of Blakey's osteosarcoma cases which would have been misclassified in terms of their fluoridation exposure. We made assumptions about the numbers of cases in each of Blakey's birth cohorts, and the peak age of diagnosis. We defined misclassified as having lived in an unfluoridated location for at least their first 8 years of life. Details of our calculations are available in the Appendix 8---B. We chose to restrict our analysis to those under age 25, since these represent about 90% of all cases in Blakey's study, and they constitute the age group for which there has been most evidence that fluoride is a risk factor. Results are shown in Table 2.

Table 2. Estimated percentage of cases misclassified as fluoridated when in fact they were unfluoridated, by birth cohort, for <25 year olds who are estimated to be 91% of all cases (age 0---49). Therefore, <25 year olds will largely determine the RRs. Estimates assume mean age of diagnosis 15, and defined as misclassified only when at least first 8 years of life misclassified.

Birth cohort	Estimated number of osteosarcomas[a]	Misclassified for at least first 8 years of life
all years	1398	33%
<1970	466	62%
1970---1979	466	38%
>1980	466	0%

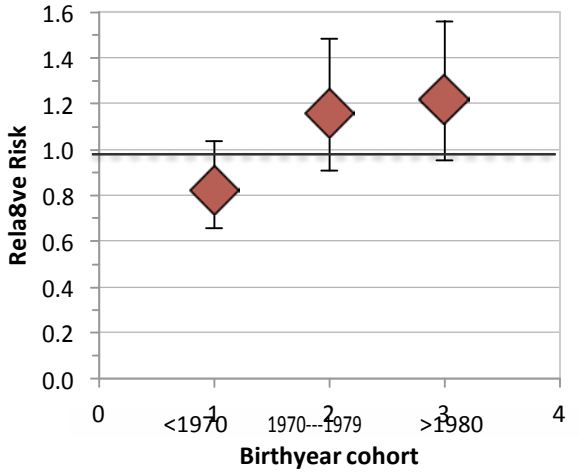
[a]Assume birth cohorts each have 1/3rd of total.

For all <25 year old subjects for all birth years, the differential misclassification is a substantial 33%. For the earliest birth cohort, misclassification is 62%. Misclassification declines with more recent birth cohorts, falling to zero with the most recent. This systematic misclassification, shifting truly non---fluoridated to fluoridated will bias Blakey's Relative Risks (RRs) downward.

Blakey's subset analyses looking at cohorts born in the periods: <1970, 1970---1979, and >1980 will not remove this bias, even for the most recent birth cohort. Although Table 2 shows 0% misclassified in the >1980 birth cohort, this is only for those under age 25, so there may be additional older cases in this birth cohort who would be misclassified.

It should be noted that the most recent birth cohort which would have the least downward bias of the cohorts has the highest RR (1.21), with the next older cohort having an RR of 1.16 and the oldest cohort, with the greatest downward bias, having an RR of 0.83. See Figure 3. This pattern is what would be expected in Blakey's results as misclassification decreased from the most recent cohorts to the earliest, if fluoridation actually increased the risk of osteosarcoma.

Figure 3. Relative Risk of osteosarcoma associated with fluoride water levels, by birth cohort, estimated by Blakey.



Misclassification is always in the direction that a truly unfluoridated case was assigned fluoridated status.

This misclassification problem is exacerbated by the fact that in the UK, fluoridated water is used by only 10% of the population. Blakey's analyses, therefore, hinge largely on just 10% of her sample

Blakey describes her findings:

> "When testing cohorts born before 1970, 1970–79 and 1980 onwards, there was no differential effect of cohort on the association between bone cancer and fluoride. An effect was not found when testing with artefactually raised levels of fluoride (Tables 2–4), nor when using narrower age---bands (0–9, 10–14 . . . 45–49 years). There was no evidence of an interaction between age---group and fluoride." [Blakey 2014]

When she says there was no differential effect of birth cohort, presumably she means none of the RRs were statistically significantly different from each other. But the point estimates clearly show a trend toward an effect. The earliest birth cohort, those more likely to be misclassified, had lowest RR and the later birth cohorts had increasing RRs.

The age bands chosen for age band analysis would not have been optimal for detecting an effect from fluoridation for ages 0---20 or 0---25. Blakey's age bands were 0---14, 15---29, and 30---49. The two younger age bands would have split the childhood cases in half, so that cell size would be about half as much as for an age band of 0---20 or 0---25, giving less power to detect an effect. The same situation would occur in the analysis when narrower age bands of 5 years were used. Each of these bands would have even smaller numbers.

Blakey does not report results of these age---band analyses other than to say they showed no association between fluoride and osteosarcoma and no interaction between age group and fluoride. Presumably, she means they showed no statistically significant associations, but due to their reduced sample sizes, that is not surprising. Furthermore, it would be interesting to see the size and direction of effects even if they did not reach statistical significance.

In summary, Blakey's exposure misclassification could have led to substantial downward bias in her effect estimates.

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4. Potential for confounding is increased in Blakey's study because in the UK, fluoridated water is not randomly distributed geographically, but is mostly in a single area. The majority of the fluoridated population lives in greater Birmingham. Therefore, any unmeasured risk factor for osteosarcoma, or inadequately controlled risk factor, stands a higher chance of confounding the relationship between fluoride and osteosarcoma. Blakey's study is mostly comparing risk in greater Birmingham to that in the rest of Great Britain. Instead of confoundin risk factors cancelling each other out when they are from a wide range of geographical areas and have different directions, there is little chance such cancelling will occur with most of the fluoridated population coming from a single geographic area.

5. Apparent misclassification of bone cancer subtypes in the West Midlands Cancer Registry, which encompassed most of the fluoridated population of Great Britain. Alternately, alteration of bone cancer numbers following reorganization of West Midlands Cancer Registry. Comparison of two sources of West Midlands cancer registry data reveals a very large discrepancy in numbers of registered osteosarcoma cases for the years 1990---1992. One data source [IARC 2002] shows large numbers of osteosarcoma cases apparently misclassified as "unspecified morphology". Such misclassification is differential rather than random, and would cause Blakey's study to miss substantial numbers of osteosarcoma cases who lived mostly in fluoridated areas. This could seriously bias the results away from a positive association between fluoride and risk of osteosarcoma. The other source of West Midlands cancer registry data we examined is that currently available from its successor agency the West Midlands Cancer Intelligence Unit (WMCIU). This is the data source Blakey used. The numbers of all bone cancers of osteosarcomas, and of "unspecified morphology" in the current WMCIU do not match those in IARC.

Investigation into the anomalies in the West Midlands cancer registry data on bone cancers. We examined data from the International Agency for Research in Cancer's (IARC) *Cancer Incidence on Five Continents* databases and website:

http://ci5.iarc.fr/CI5plus/Pages/download.aspx

The full, detailed database of individual cancer registrations is available for downloading. Most of the data is also available for online creation of graphs and tables at:

http://ci5.iarc.fr/CI5plus/Pages/online.aspx

The IARC obtained individual level data directly from the cancer registries within a few years of the end of each survey period. The IARC performed their own extensive quality control checks [IARC 2002, Chapter 6]:

> "Chapter 6, on Processing of Data, makes it clear that an extensive process of verification of coding, identifying possible duplicate registrations, querying unlikely or impossible combinations of codes, and conversion to a standard format has been carried out, before any tabulations are prepared for editorial evaluation. These steps in validation of the data are part of the routine to which the great majority of data-sets are subjected, and the fact that it has been completed more or less successfully forms part of the editorial evaluation."

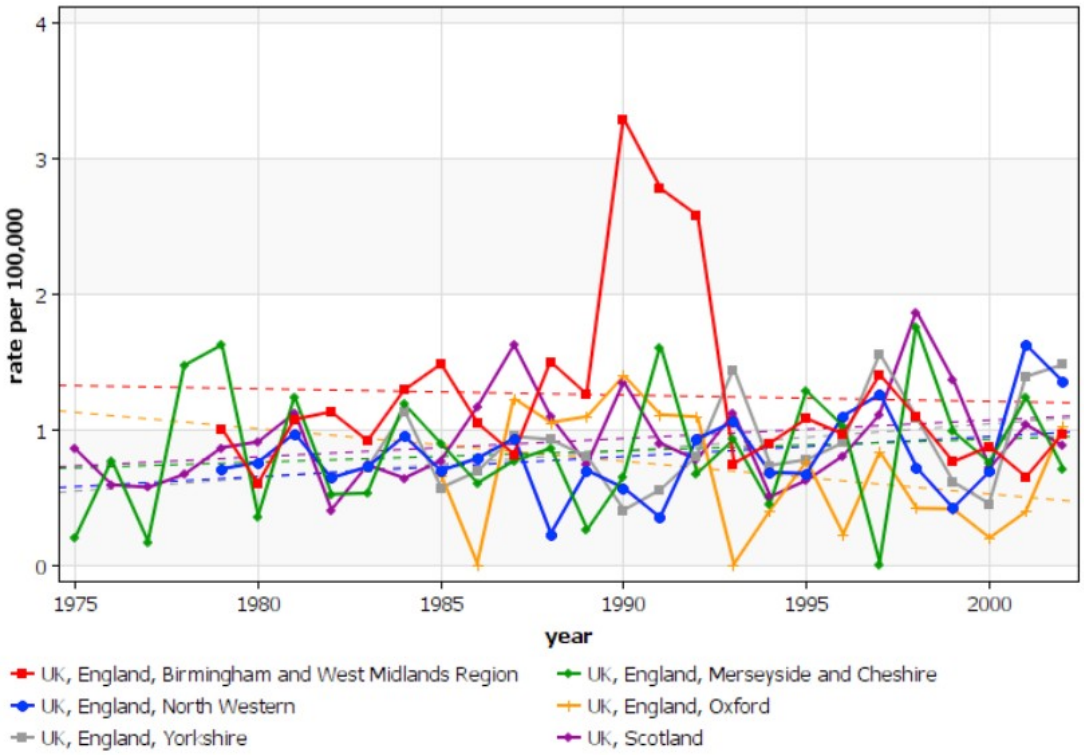
For the West Midlands Cancer Registry, for the time period in question, the IARC identified problems due to an unusually high number of tumors lacking morphological verification, which could have led to excessive numbers of "unspecified morphology" [IARC 2002; p. 480, 711].

The IARC online access uses the same data and can create graphs and tables online, but does not allow subclassification of cancer type that are available in the downloadable full dataset. For example, the online data only has "C41 bone", rather than the eight subclassifications "osteosarcoma", "Ewing sarcoma" ... "unspecified morphology". Nevertheless, the online service is quicker than doing the programming and graph drawing using standalone software, so we used it to perform several checks on the IARC dataset for the West Midlands Cancer Registry.

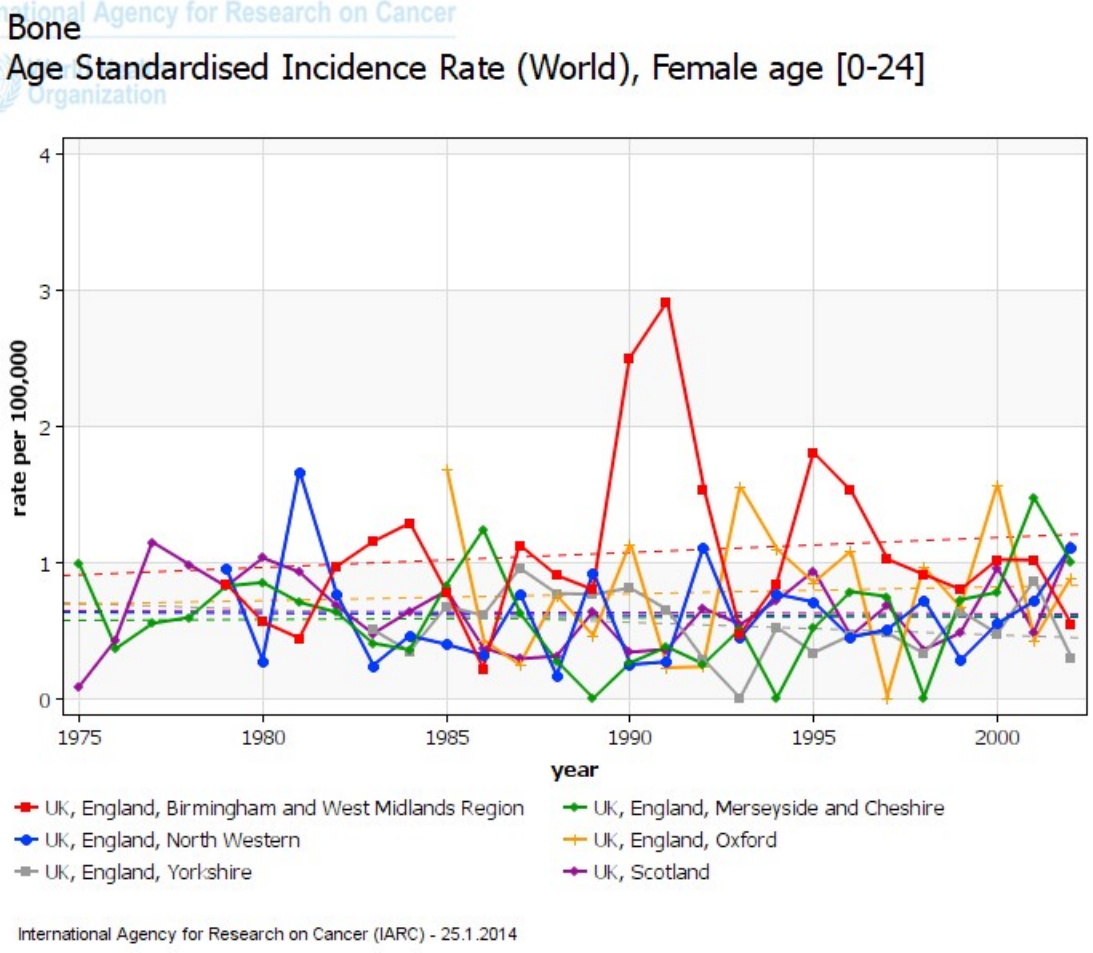
We looked to see whether any other UK cancer registry showed a similar short---term spike in bone cancers at any time. None do. Graphs of the time trends for all six available UK cancer registries for bone cancers in males and females age 0---24 are below. The red line is West Midlands and the dramatic peak during 1990---1992 is remarkable. Nothing else like it occurs in any other registry. It occurs for both males and females. These are age---standardized rates (ASRs), with separate graphs for males and females:

Bone

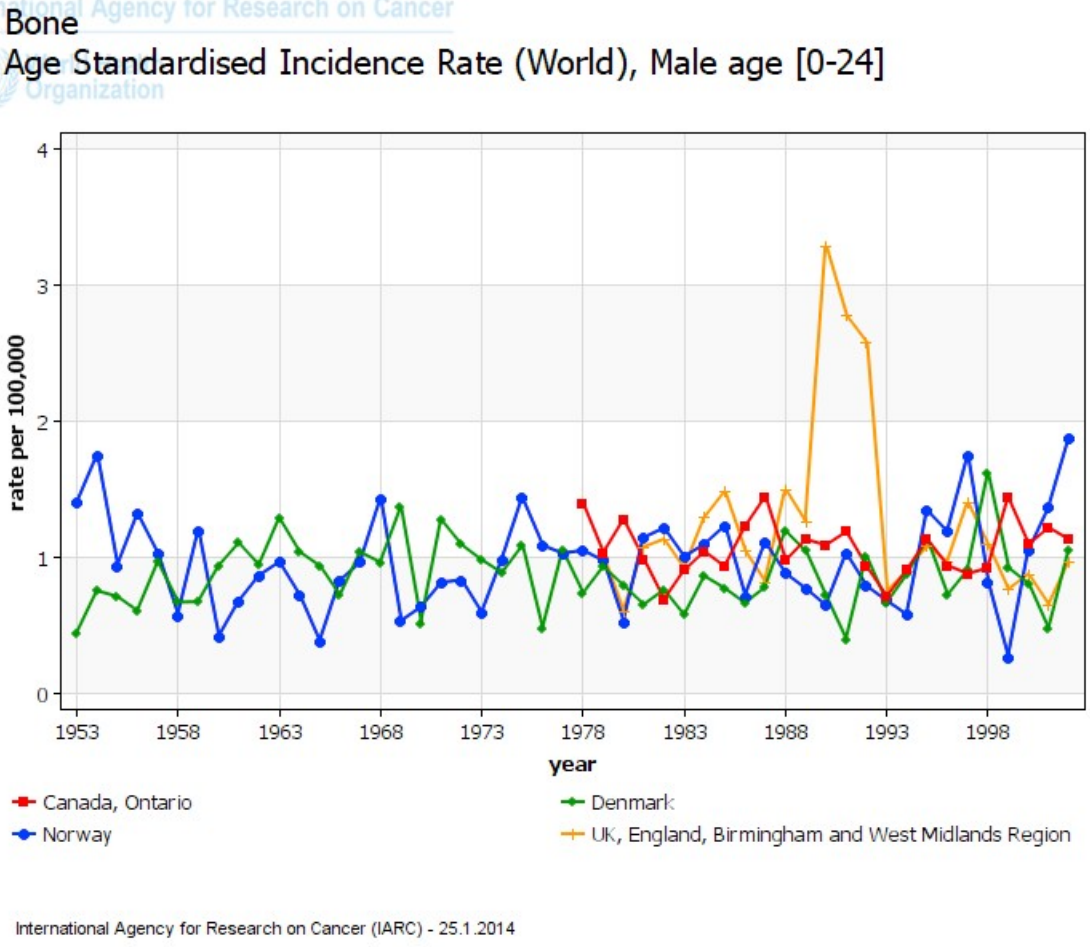
Age Standardised Incidence Rate (World), Male age [0-24]



International Agency for Research on Cancer (IARC) - 25.1.2014

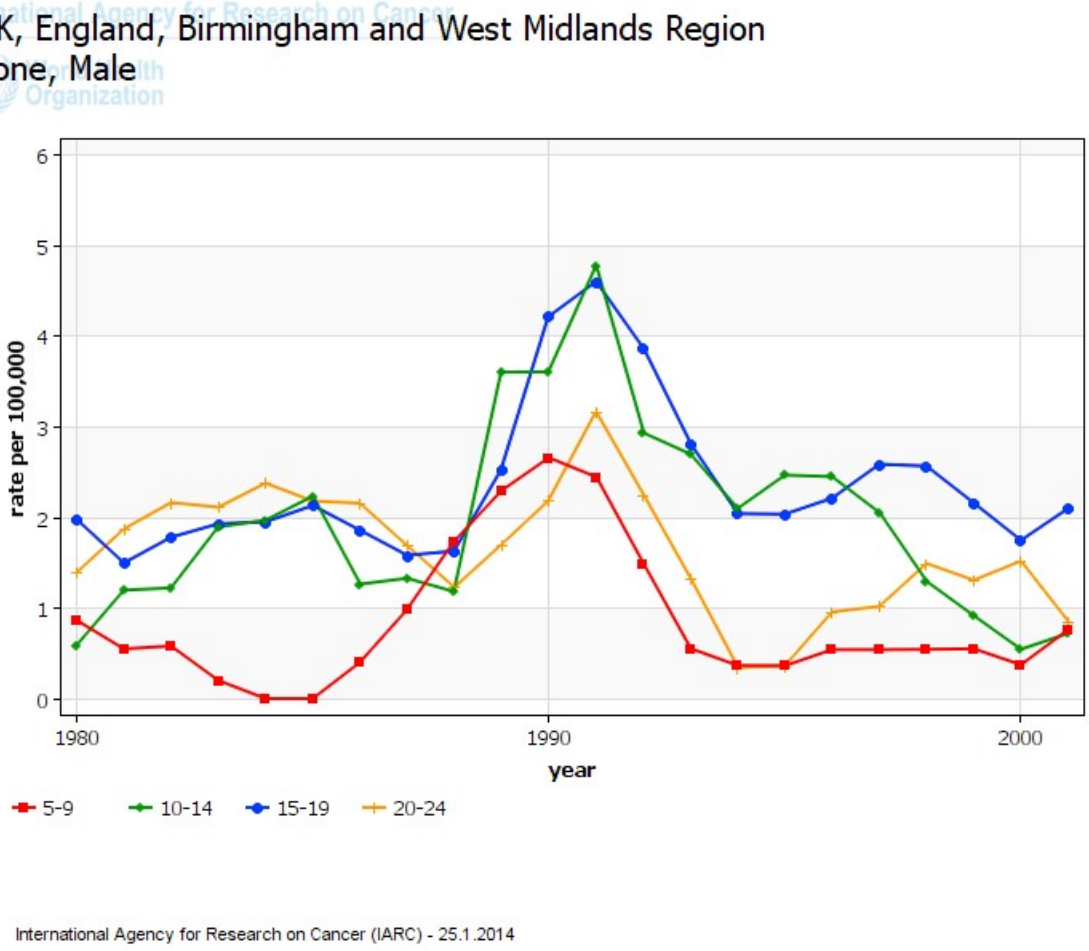


We also compared West Midlands to several high quality cancer registries from around the world which had fairly similar populations (Ontario, Canada; Denmark; Norway). Below is the graph of the results.

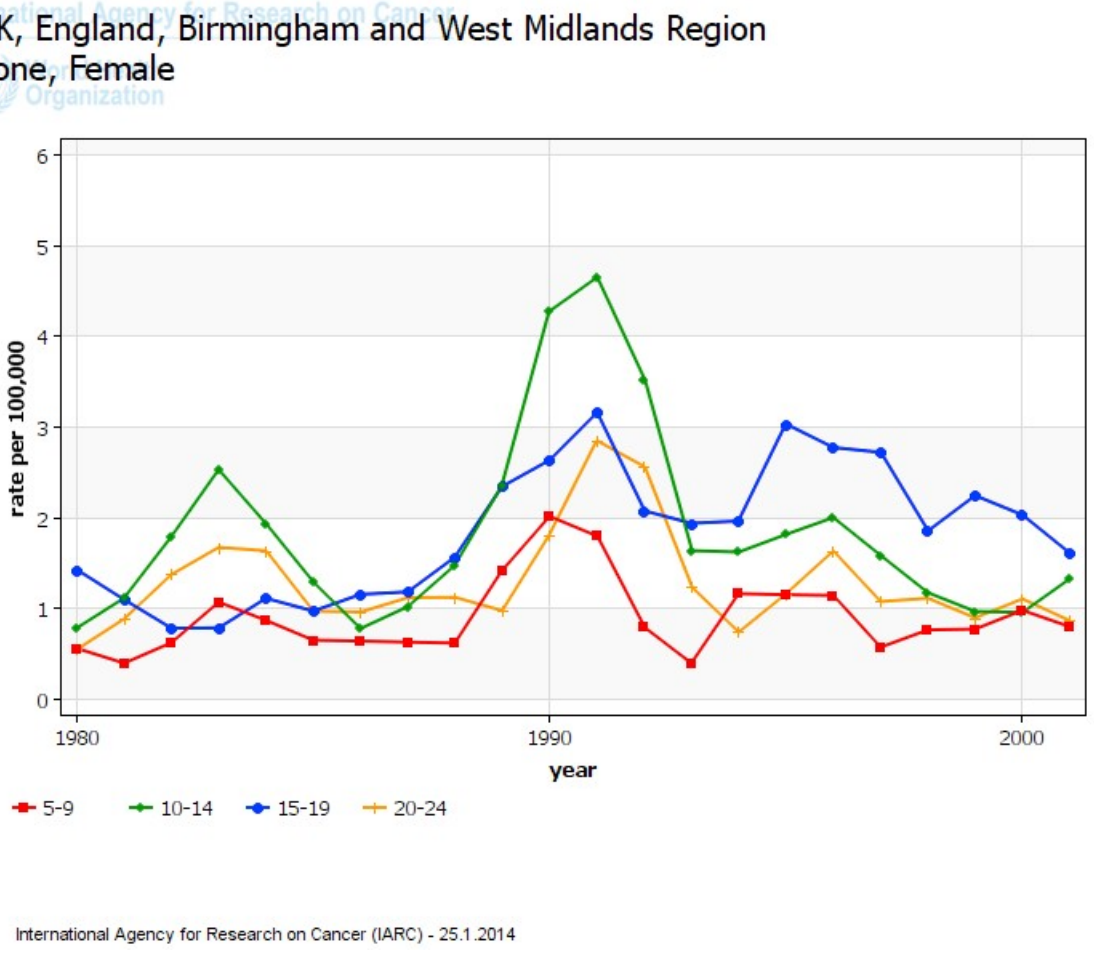


In no registry that we examined did we ever find a similar clear spike in bone cancer rates as in West Midlands (shown here in yellow), at any time period.

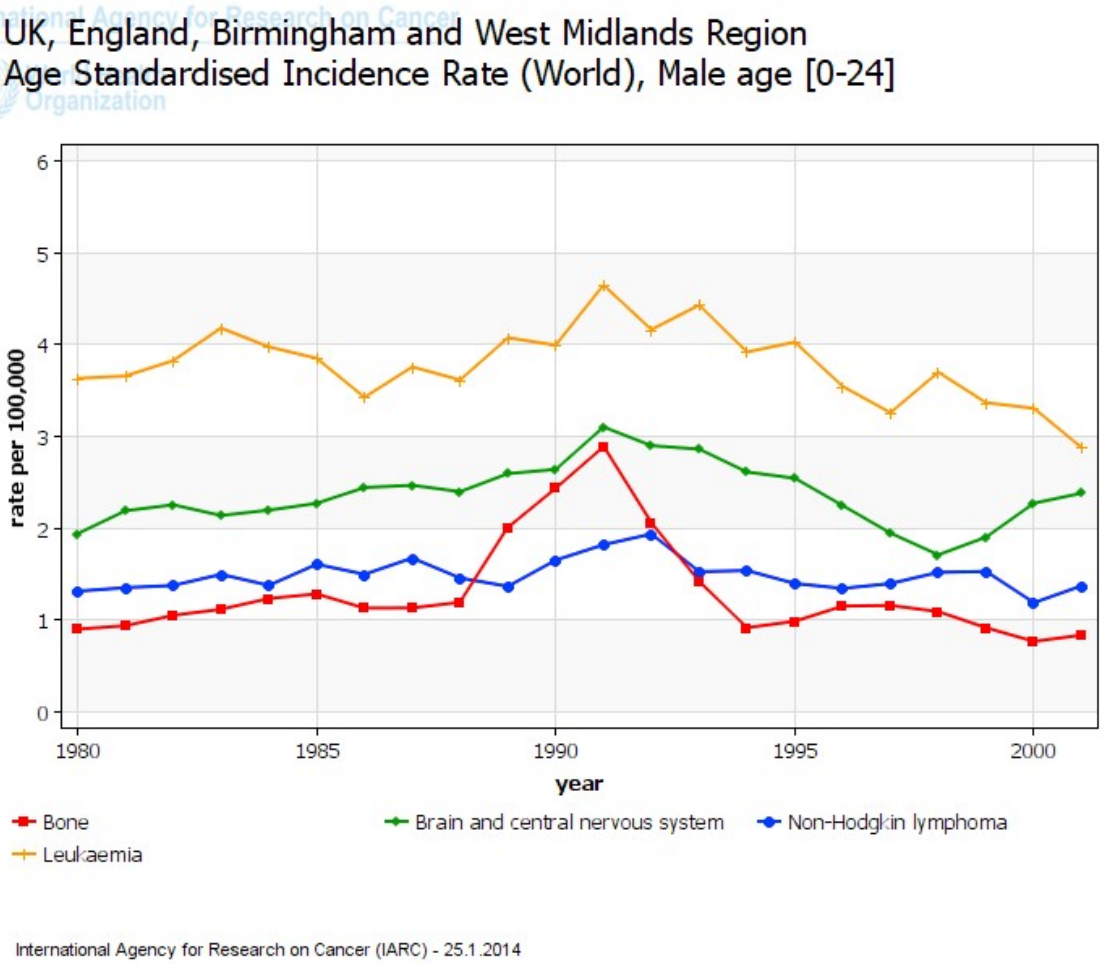
Looking with more detail at West Midlands, here is the graph showing how the spike occurred for each 5---year age band from ages 5---24. This graph used 3 year averaging for smoothing.



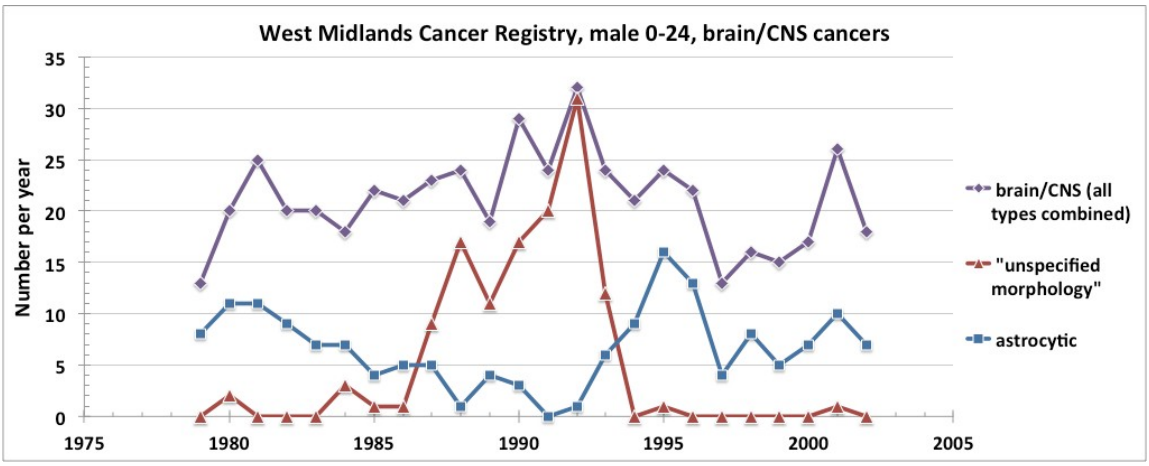
All age groups show a spike in rate, but it appears the youngest age group might have peaked before the older age groups. The age 5---9 group reaches a peak in 1990 while the others reach a peak in 1991. The same pattern is seen for females:



We checked whether any other types of cancer spiked at the same time as bone cancer in West Midlands. We focused on cancers that occur at appreciable rates in children. Leukemia brain/CNS, and non---Hodgkin's lymphoma all appear to show a modest peak rate in 1991 compared to the average of all the other years available. These multi---cancer graphs are ASRs smoothed with 3---year averages. The sharp peak in childhood cancers between 1990---1992, especially for bone cancers, suggests a space---time cancer cluster occurred in West Midlands during this time period. Since all the cancer types were rare, it is not surprising that such a cancer cluster was apparently not recognized. Recent work by McNally [2009] has found that childhood osteosarcoma in England has a fairly strong tendency to occur in space---time clusters. The very high rates of childhood bone cancer in the West Midlands in 1990---1992 might be just such a cluster.



The IARC downloadable database contains the data for all the subtypes of cancer groupings so we investigated possible misclassification for other childhood cancers. Some types appear to have the same misclassification into "unspecified morphology" as the bone cancers. In particular, for the brain/CNS group, the astrocytic subgroup appears to have been misclassified as "unspecified morphology" during the period 1988---1994. When the "unspecified morphology" peaked, the astrocytic dropped, as can be seen on this graph:



The leukemia subclassification of ALL showed a more distinct peak for the youngest age groups than is shown in the previous graphs for all leukemia. This would be consistent with McNally's finding that ALL in 1---4 year olds had a stronger tendency to occur in space---time clusters than other age groups or subtypes [McNally 2006].

No other cancer types besides bone, leukemia, brain/CNS, and non---Hodgkin's lymphoma appear to have peaked around 1990---1992 in West Midlands.

The time trends for these multiple types of childhood cancer, not just bone cancers, all of which have been shown to have a propensity for space---time clustering [McNally 2009], and all peaking around 1990---1992 suggest that this was a real space---time cluster, and not just erroneous data due to some error at the West Midlands Cancer Registry.

The implication for Blakey's study is that, if she used the same data as was given to IARC, she would have missed approximately 90 osteosarcomas, most in the age group 0---24, and all in widely fluoridated West Midlands, because they would have been misclassified as "unspecified morphology". Our estimate of 90 missing osteosarcomas is calculated by adding the males and females with "unspecified morphology" and assuming that the majority of these misclassified should have been osteosarcomas. Blakey had roughly 2000 osteosarcomas for ages 0---24, male plus female. Great Britain is roughly 10% fluoridated, so roughly 200 of Blakey's osteosarcomas would have been in fluoridated locations if the incidence rates were similar in fluoridated and non---fluoridated locations. An adding of 90 osteosarcoma cases in fluoridated locations to those 200 is substantial enough that it could change Blakey's results from null to a statistically significant positive association.

It is also possible that the West Midlands cancer registry's data was altered between the time it was given to the IARC and the time that Blakey received it. The IARC received individual case level data sometime between 1993 and 1997. The West Midlands Cancer Registry was reorganized in 1995. Blakey received data from the West Midlands Cancer Intelligence Unit (WMCIU), the successor to the West Midlands Cancer Registry, some time between 2005 and 2010. The data for

both IARC and Blakey were records for individuals. From inquiry to WMCIU for numbers of all bone cancers and osteosarcomas for each year from 1979 – 2002, we received numbers of bone cancers that were very close to the IARC numbers for all years except 1990---1992. The IARC data showed a sharp spike in bone cancers for these years, but WMCIU did not. The WMCIU did show an unexplained anomaly in numbers of osteosarcomas in the year 1990, when its numbers dropped dramatically compared to all other years.

Since Blakey used the current WMCIU data, she would have missed a substantial number of osteosarcomas from West Midlands if the WMCIU data was erroneous. The number missin would be somewhat less than the 90 missing cases if she had used the IARC data that appeared to suffer from extreme misclassification of osteosarcomas to "unspecified morphology".

It should be noted that there is at least one instance where a UK cancer registry was reorganized and comparison of numbers before and after reorganization showed some substantial differences. In the Wales cancer registry, numbers of leukemias in certain locations changed substantially between data released before the reorganization and that released after reorganization [Busby 2007]. No explanation for these leukemia number differences was given by the cancer registry.

The important conclusion is that if West Midlands cancer registry cases were misclassified in the time around 1990---1992, or if it was altered at some time after about 1992, then Blakey would have had substantial differential misclassification affecting mostly the fluoridated parts of Great Britain. This would have led to Blakey's estimates for the association between F and osteosarcoma being biased away from a positive effect.

6. Did not control for radon exposure, which has been found to be a risk factor for childhood osteosarcoma in a recent study. Blakey did not consider indoor radon, a risk factor for osteosarcoma identified in one case---control study in Cornwall, England [Wright & Pheby 2004]. If radon is a risk factor for osteosarcoma throughout Great Britain, then correction for radon would have reduced bias toward the null and would result in a higher risk ratio.

Radon may also bias an effect away from a positive association, potentially even toward a spurious protective effect of fluoride on osteosarcoma. The main fluoridated regions of West Midlands and North East both both have low or very low radon levels, while some of the non---fluoridated parts of Great Britain have high to very high levels of radon [Miles 2007, http://www.ukradon.org/information/ukmaps].

Summary

The absence of information on the history of fluoride exposure, coupled with assignment of fluoride exposure based solely on 2004---2006 water fluoride levels, likely biased Blakey's effect estimates toward null or even away from a positive effect. No age---specific exposure analyses were

possible with Blakey's data, which would also bias her effect estimates toward the null, if Bassin's [2006] finding of a strong exposure age---specific effect is real.

Studies have shown that total F intake in Great Britain, especially in years before about 1980, was very similar between fluoridated and non---fluoridated areas. This is likely due to the high consumption of tea, even in young children, which overwhelms the exposure contribution from fluoride in water. The period before 1980 was the most relevant to exposure risk for osteosarcoma.

Evidence suggests there may have been errors in the West Midlands cancer registry data used by Blakey. This registry would contain the majority of people in Great Britain with fluoridated water. The error was apparent misclassification of osteosarcomas as "unspecified morphology" which excluded them from Blakey's study. Another possible error may have been the omission of a substantial number of bone cancer or osteosarcoma cases in the West Midlands cancer registry data.

The possible errors were for the years around 1990---1992. If either of these errors in fact occurred, Blakey's data would have missed substantial numbers of osteosarcoma cases from the mostly fluoridated West Midlands area. Thus, her effect estimates would have been biased away from finding a positive effect.

Given all these potentially serious limitations of the Blakey study, her conclusion that the study is evidence of "no effect" of fluoride on osteosarcoma risk is an overstatement. Blakey's study design and data may have been insufficient for her to detect a risk from fluoride, even if one exists.

In fact, in the one model restricted to those with the least exposure misclassification (birthyear cohort of those born after 1980), Blakey did find a non---significant effect. This is consistent with Young's very similar study of much the same population [Young 2015]. So, these two studies actually are consistent with studies which have found an effect of fluoride increasing osteosarcoma risk, rather than being evidence that no such effect exists.

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