A BRIEF REPORT ON THE ASSOCIATION OF DRINKING WATER FLUORIDATION AND THE INCIDENCE OF OSTEOSARCOMA AMONG YOUNG MALES

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NEW JERSEY DEPARTMENT OF HEALTH
A BETTER STATE OF HEALTH

Environmental Health Service

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EXECUTIVE SUMMARY

It is well known that fluoride provides important public health benefits by effectively preventing dental caries in children. The Public Health Service (1991) endorses artificial fluoridation of drinking water at a concentration of 0.7-1.2 milligrams of fluoride per liter of water (or parts per million) as the optimally beneficial level for preventing dental caries. The U.S. Environmental Protection Agency (USEPA) allows up to 2 parts per million for artificial fluoridation and up to 4 parts per million for naturally-occurring fluoride (National Primary Drinking Water Regulations, 40 CFR 141.11 and 143.3). Other potential sources of fluoride ingestion include food, vitamins, and swallowed toothpaste.

Recently, a national study of drinking water fluoridation at the county level found a significant association with osteosarcoma incidence among males under 20 years of age (Hoover et al., 1991). However, the meaning of the association was questioned by the authors because of the absence of a linear trend of association with the duration of time for which the water supplies were fluoridated. Furthermore, the simple study design used did not have individual information on the average amount of water ingested daily, use of dental fluoride supplements, long term residence, other potentially confounding (or causal) exposures, or genetic involvement.

As a follow-up to the study by Hoover et al., a small study of similar design was initiated by the New Jersey Department of Health to compare drinking water fluoridation at the municipal level with the municipal residence of osteosarcoma cases at the time of diagnosis. No interviews were conducted and data on individual residential history, average amount of water ingested, use of dental fluoride supplements, exposure to other carcinogens and familial cancer history were not available. In addition, the total number

of cases was small. Therefore, observations should be interpreted cautiously because: 1) exposure misclassification could lead to under- or overestimation of effects, 2) unmeasured confounding by other potential causes of osteosarcomas could introduce bias leading to under- or overestimation of effects of exposure, and 3) an observed association could be due to chance.

Osteosarcoma incidence between 1979 and 1987 was compared by ecologic epidemiology methods to water supply fluoridation in seven counties in central New Jersey. Twelve cases were diagnosed among males under age 20 in fluoridated municipalities vs eight cases in non-fluoridated municipalities. The rate ratio of incidence in fluoridated vs non-fluoridated municipalities was 3.4 with a 95% statistical confidence interval (95%CI) between 1.8 and 6.0. All twelve cases in fluoridated municipalities resided in a three county area with the greatest prevalence of fluoridation. The rate ratio of incidence in fluoridated vs non-fluoridated municipalities in the three county area was 5.1 (95%CI 2.7-9.0). Among 10-19 year old males in those three counties, the rate ratio was 6.9 (95%CI 3.3-13). No other age/sex groups exhibited significant association with fluoridation.

Because of the limitations of the study design and the small numbers of cases that occurred, this analysis does not imply a causal connection between fluoridation and osteosarcoma. From a public health perspective, the findings are not sufficient to recommend that fluoridation of water supplies be halted, but do support the importance of investigating the possible link between osteosarcoma and overall ingestion of fluoride. In addition, it is recommended that dentists identify whether children reside in fluoridated communities and appropriately advise on fluoride supplementation.

INTRODUCTION

Osteosarcoma is the most common primary malignant tumor of the bone and is one of the principal cancers of childhood, although it is rare (2.9 per million average annual overall incidence rate in New Jersey) and only represents 0.2% of all primary cancers (Malawer et al., 1989). Under age 20, it affects males more than females.

Other than ingestion of certain radioisotopes, like radium-226 and -228, or exposure to high doses of x-rays (reviewed in National Research Council, 1988, 1990), there is no known cause of osteosarcoma.

Etiologies may vary in different age groups. For instance, increased osteosarcoma incidence around puberty may be linked to rapid bone growth (Price, 1958; Glass and Fraumeni, 1970; Larsson and Lorentzon, 1974; Polednak et al., 1984). Among older adults, Paget's disease is associated with osteosarcoma incidence (Polednak et al., 1984).

Several other risk factors have been proposed. Possible viral involvement has been noted in laboratory animals (Finkel, 1975), but not among humans (Operskalski et al., 1987). In addition, a small number of cancer families include individuals with osteosarcoma (Coyler et al., 1979; Operskalski et al., 1987), indicating a potential role for genetic propensity. Among the chemical candidates are vinyl chloride, beryllium compounds, and fluorides. Beryllium compounds have produced osteosarcomas in rabbits, but the risk for humans has not been shown (IARC, 1980). Vinyl chloride has produced osteosarcomas in rats, but only benign bone lesions in humans (IARC, 1979). During the last twenty years a number of epidemiologic studies using ecologic or case-control methods did not find an association between bone cancer mortality and fluoridation (Kaminsky et al., 1990). However, in addition to the problems associated with death certificate registries, most

studies either used large aggregate areas, such as counties, and/or did not provide separate information on childhood mortality. Recently, a national ecologic epidemiology study of drinking water fluoridation at the county level found a significant association with osteosarcoma incidence among males under 20 years of age (Hoover et al., 1991). However, the meaning of the association was questioned by the authors because of the absence of linear trend of association with duration of time the water supplies were fluoridated.

A study of tumor induction in rodents suggested that fluoride can cause osteosarcoma, although this was not the conclusion of the reviewing scientific panel (National Toxicology Program, 1990), who concluded that borderline statistical significance and issues about fluoride levels in the feed of rodents constituting the "historical" control group prevented the use of this study as evidence about carcinogenicity of fluoride.

Potential sources of fluoride exposure include food, vitamins, swallowed toothpaste, and drinking water. The Public Health Service (1991) endorses 0.7-1.2 milligrams of fluoride per liter (parts per million) as the optimally beneficial level of for preventing dental caries. The U.S. Environmental Protection Agency (USEPA) and the New Jersey Department of Environmental Protection and Energy (NJDEPE) allow up to 2 parts per million for artificial fluoridation and up to 4 parts per million for naturally occurring fluoride (National Primary Drinking Water Regulations, 40 CFR 141.11 and 143.3).

Based on the study by Hoover et al. (1991), a small study of relatively simple design was conducted by the NJDOH. (It should be noted that the study was not initiated because of cancer cluster concerns.) It was based solely on the address of osteosarcoma cases at the time of diagnosis. No interviews were conducted and data on individual residential and exposure histories were

not available. The study observed an association between fluoridation of water and osteosarcomas among males under 20 years of age in seven Central New Jersey counties.

METHODS

Case Ascertainment

Incident cases of osteosarcoma were compiled from the New Jersey Cancer Registry (NJSCR) for the years 1979-1987. New Jersey law requires mandatory reporting to the NJSCR and agreements with hospitals in neighboring states insures completeness. Available information includes age, race, sex, and address at the time of diagnosis. The 1980 U.S. Census was the source of population data on a municipality level for the calculation of annual rates. To check on the possibility that significant population shifts skewed the rates between 1980 and 1990, the 1983 (study period midpoint) and 1987 (last year of the study) populations were calculated by proportionately interpolating the 1990 U.S. Census with the 1980 Census. In the seven county and three county study areas (see below), the relative population shifts from fluoridated to unfluoridated areas are estimated to have been 2-4% in 1983 and 4-8% in 1987. This includes the effect of migration into and out of the study area as a whole.

Exposure Assessment

Information on fluoridation of drinking water supplies on a municipality level was received from the NJDEPE. In New Jersey individual municipalities have authority to decide whether to implement fluoridation. Seventy municipalities in New Jersey received fluoridated water for at least part of the year as of the early 1970's. In addition, water supplies on three military bases and one hospital in four other municipalities are fluoridated. The overall prevalence of fluoridation in New Jersey is 15% of the population.

For this analysis, municipalities were considered "fluoridated" if greater than 85% of the population was supplied with fluoridated water from at least the early 1970s until at least 1987. (In practical terms, this meant

that if private wells supplied more than 15% of the population in a municipality with a fluoridated public water supply, the municipality was excluded from the analysis.) Municipalities were considered "non-fluoridated" if less than 10% of the population was supplied with fluoridated water. Municipalities with mixed supplies due to partial bulk purchase were excluded from the computations. Non-fluoridated municipalities seasonally augmented with bulk-purchased fluoridated water were also excluded. Municipalities with the fluoridated military bases were also excluded.

Municipalities in ten New Jersey counties account for all of the eligible artificially fluoridated municipalities. Part of Gloucester County is naturally fluoridated and is analyzed separately (see below). However, 98% of the population in eligible municipalities receiving artificially fluoridated water reside in seven central New Jersey counties: Atlantic, Burlington, Mercer, Middlesex, Monmouth, Somerset and Union Counties. (The remaining municipalities are small and mostly in parts of the State geographically separate from the central New Jersey study area.) Furthermore, almost three-quarters of the fluoridated population in New Jersey resides in a contiguous three county area (Mercer, Middlesex and Monmouth Counties).

Of 91 municipalities in the three counties, twelve were ineligible and excluded from analysis. Of the remaining municipalities in the other four counties, twelve were excluded. In the seven counties, all but three of the currently fluoridated supplies became fluoridated between the 1950s and the early 1970s. Among the other three municipalities, one began fluoridation in the late 1970s, one in 1989 and one in 1990. The water supply that began fluoridation in the late 1970s was excluded from analysis, while the other two were categorized as unfluoridated. Two other water companies ended fluoridation in 1980 and 1985 and were also excluded from the analysis. Only

two cases resided in municipalities excluded from analysis, yielding no major effect on results.

In Gloucester County there are thirteen municipalities whose public water supplies draw from a formation producing water containing fluoride in the 0.5-3.3 ppm range (nine were under 2.0 ppm). In eleven out of the thirteen municipalities, public supplies provide water for more than 85% of the population. (In addition, in one of the eleven a third of the municipal population is supplied by a second water company that provides artificially fluoridated water.) Since the boundary of the natural fluoridation is not clear, only the eleven municipalities were included in the analysis.

The USEPA Toxic Release Inventory Database from 1988 was received from NJDEPE. Carcinogenic compounds released to the air were totaled by municipality. The compounds were categorized as carcinogenic if they are classified as known, probable or possible human carcinogens by USEPA.

Statistical Analysis

In the present analysis, the relative rate ratios were determined for osteosarcoma rates in fluoridated vs non-fluoridated areas. The confidence intervals were calculated using tables from Haenszel et al. (1962).

RESULTS

In New Jersey between 1979 and 1987, 116 and 78 cases of osteosarcomas among males and females, respectively, were reported to the New Jersey Cancer Registry. Under age 20 there were 51 and 37 cases, of which 45 and 33 were between ages 10 and 19. During 1979-1987 the average annual rates in the 10-19 age group were 7.6 per million and 5.8 per million, respectively.

Seven County Study Area

In the seven county study area, irrespective of study eligibility (see Methods), there were 22 males and 10 females under age 20 diagnosed with osteosarcoma. In the eligible fluoridated municipalities, there were 12 males under age 20 diagnosed with osteosarcoma, an average annual rate of 11.9 per million. In the eligible non-fluoridated municipalities the rate was 3.5 per million, based on eight cases. (Two occurred in excluded municipalities.) The incidence rate ratio between fluoridated vs non-fluoridated municipalities was 3.4 with a 95% confidence interval (95%CI) of 1.8 to 6.0. Seventeen of the 20 male cases were between ages 10 and 19 (Table 1) with the same rate ratio, 3.4 (95%CI 1.7-6.4). Among white males in the 10-19 age group the rate ratio was 4.8 (95%CI 2.3-8.8).

Rate ratios were not elevated among females or among men in older age groups.

Three County Study Area

All 12 cases among males under age 20 in the fluoridated municipalities of the 7 counties were residents of fluoridated municipalities in the three county sub-area at the time of diagnosis (Table 2). The average annual rate among males under 20 in this subgroup of fluoridated municipalities was 14.9 per million. Three cases occurred in non-fluoridated municipalities in the

three county area, giving an average annual rate of 2.9 per million. The rate ratio of osteosarcoma incidence among males under 20 in fluoridated vs non-fluoridated municipalities of the three county area was 5.1 (95%CI 2.7-9.0). For males between ages 10 and 19 the rates in fluoridated and non-fluoridated areas were 22.0 per million and 3.2 per million, respectively, yielding a rate ratio of 6.9 (95%CI 3.3-13). Among white males in this age group the rate ratio was 8.0 (95%CI 3.9-15). When the rate in the fluoridated municipalities in the three counties was compared with the State rate for males aged 10-19, the RR was 2.9 (95%CI 1.4-5.3).

The average annual rate for osteosarcoma among males under 20 in the three county study area, irrespective of fluoridation, was 8.5 per million, yielding an RR of 1.7 (95%CI 1.0-2.8) for these counties when compared with the State rate. If the three counties are removed from the State rate calculation for this age/sex group, the State average annual rate becomes 4.2 per million. The RR of osteosarcoma in the three counties compared to the State rate excluding those three counties is 2.0 (95%CI 1.2-3.2).

Gloucester County and Naturally-Occurring Fluoride in Drinking Water

Only one case of osteosarcoma was reported among males between ages 10 and 19 from the municipalities in the naturally fluoridated area of Gloucester County during the study years, yielding an average annual rate of 9.7 per million. (In addition, only one case in this age-sex group was reported in municipalities believed to be largely free of natural fluoridation, but was not included in the analysis, as discussed in the Methods). If the artificially fluoridated municipalities of the seven county study area and the naturally fluoridated municipalities of Gloucester County are analyzed together, the combined rate for the 10-19 year old males is 16.4 per million and the RR is 3.2 (95%CI 1.6-5.8).

Assessment of Potential Confounding by Other Factors

The relative contribution of ground water and surface water was compared between fluoridated and non-fluoridated municipalities. Among the fluoridated municipalities of both the seven and the three county study areas, surface water supplied about 65% of the male population under 20 and the municipalities where 7 out of the 12 cases resided. Mixed ground water and surface water sources supplied an additional 15% of the fluoridated male population under 20 and the municipalities where 1 out of the 12 cases resided. Ground water supplied 20% and the municipalities where 4 out of 12 cases resided. In the non-fluoridated municipalities of both the seven and the three county study areas, surface water supplied 10% of the male population under 20 (1 out of 8 cases), ground water supplied 55% (4 out of 8 cases), and mixed ground and surface water sources supplied an additional 35% (3 out of the 8 cases). Gloucester County was entirely supplied by ground water. Thus, no clear pattern was clearly discernable. In addition, an analysis of osteosarcoma among males under 20 in the thirteen counties outside the study area found no relationship with the source of water.

To explore a potential association between air toxics and childhood osteosarcoma, the USEPA Toxic Release Inventory Database from 1988 was examined. It did not provide any support for this hypothesis.

DISCUSSION

This study is very limited because no interviews were conducted and data on individual residential history, average amount of water ingested, use of dental fluoride supplements, exposure to other carcinogens and familial cancer history were not available. In addition, the total number of cases was small. Therefore, the observations should be interpreted cautiously because: 1) exposure misclassification could lead to under- or overestimation of effects, 2) unmeasured confounding by other potential causes of osteosarcomas could introduce bias leading to under- or overestimation of effects of exposure, and 3) the observed association could be due to chance.

The results of this study of osteosarcoma incidence between 1979 and 1987 in the seven central New Jersey counties with artificially fluoridated municipalities suggest that incidence among males between 10 and 19 years old is associated with fluoridation on a municipality level. Among males in this age group there were 10 cases from fluoridated municipalities, compared to seven in the non-fluoridated area with a rate ratio of 3.4 (95%CI 1.7-6.4). No other age/sex group exhibited a significant association with fluoridation. It should be noted that even if these observations represented a causal relationship, less than one additional case per year would be attributed to water fluoridation in New Jersey, based on a population attributable risk proportion of 0.41 (Levin, 1953, cited in Markush, 1977).

Other than radium, high doses of x-rays, and genetic propensity, the etiology of osteosarcoma has not been characterized and there are no additional strong hypotheses. Fluoride exposure is one possible explanation, though others have been proposed.

There has been recent evidence that high concentrations of fluoride (79 ppm or 3.9 mg/kg) in water are marginally significantly associated with the

incidence of osteosarcoma in male rats (National Toxicology Program, 1990). There was no excess osteosarcoma in rats drinking water with 11 ppm of fluoride. These results were not validated by the scientific advisory panel reviewing the data because the cancer excess was marginally significant, because of issues about fluoride levels in the feed, and because mice were not affected. Another study of mice and rats found no evidence of carcinogenicity, but was flawed by inadequate control of diet and incomplete examination of tissues (Carcinogenicity Assessment Committee, 1990). Other data indicate that fluoride is not mutagenic or genotoxic; however, a role as a promoter during bone growth has not been excluded.

If rapidly growing bone in adolescent males is most susceptible to the development of osteosarcomas (Glass and Fraumeni, 1970), it is possible that fluoride acts as a cancer promoter during a narrow window of susceptibility. The interplay of hormonal influences and the intensity of the growth spurts may be potent influences. Since fluoride is toxic to cells and a variety of enzymes at high concentrations (reviewed by Kaminsky et al., 1990; and Public Health Service, 1991), it may exert tumor promoting effects in the osteoblast cell microenvironment during bone deposition. Genetic predisposition may also play a role.

A recent national ecologic study of fluoridation at the county level also found an association of osteosarcoma incidence (1973-1987) with fluoridation (Hoover et al., 1991). While elevated rates were observed among young males in fluoridated areas (a summary rate ratio of 1.43, 95%CI 1.16-1.76, was computed from presented data), it was concluded that the association was not biologically significant because of the absence of linear trend of association with duration of time the water supplies were fluoridated. Since individual residential history was unavailable, this trend test was based on the

assumption that the cases lived their entire lives at the same residence as at the time of diagnosis. A similar, unreported analysis in the current study found that all cases in the fluoridated study area would have been exposed to fluoridated water their entire lives if the same residency assumption is made. However, if fluoride acts as a cancer promoter during periods of bone growth, rather than an initiator, the duration/latency issue may not be pertinent. The Hoover et al. study considered counties fluoridated if greater than 60% of the population were served by fluoridated supplies. In comparison, the current study probably has less exposure misclassification because it required 85% of the population to be served by fluoridated supplies for a municipality to be classified as fluoridated. This type of non-differential misclassification tends to weaken the associations that are observed (Brenner et al., 1992).

Ecologic studies, including the present one, do not have individual information on average amount of water ingested daily or long-term residence or other sources of fluoride in the diet. However, if the exposure of interest is a promoter, then the long-term residency information may not be as important. In addition, there may have been less misclassification due to incomplete or inaccurate residency information in the three county portion of this study than in the seven county study area, since the geography of fluoridation suggests that local relocation within the three counties would tend to keep families within fluoridated or non-fluoridated areas. This hypothesis is consistent with a higher rate ratio in the three counties than in the overall seven counties.

Since all cases among males under 20 occurred in the three county study area, there may have been other exposures that contributed to development of the osteosarcomas. However, the estimated pounds of carcinogenic compounds

released to the air around industrial and commercial sites in each municipality (derived from the USEPA Toxic Release Inventory, 1988) were not associated with the incidence of osteosarcoma. Another possibility is that other chemicals in water may provide a necessary co-factor for any effects of fluoride. However, there were no obvious candidates and there was no discernable relationship between the source of water and osteosarcoma incidence.

Drinking water is one source of fluoride exposure, but other sources include food, swallowing of toothpastes containing fluoride, and the use of prescribed fluoride tablets (Kumpulainen and Koivistoinen, 1977; Public Health Service, 1991). Ingestion of toothpaste and fluoride supplements by children may be responsible for as much intake of fluoride as drinking fluoridated water (Heifetz and Horowitz, 1986; Kaminsky et al., 1990). One survey found that dentists prescribe more fluoride supplementation in fluoridated areas than in non-fluoridated areas (Margolis et al., 1980). However, elevated ingestion of water during the summer months, or in conjunction with sports activities, may also be responsible for increased fluoride uptake. In addition, there have been reported incidents in the U.S., though not in New Jersey, where malfunctioning equipment over-fluoridated water systems, occasionally leading to acutely toxic results (National Center for Preventive Services/Division of Health, 1992). There may be many more unreported incidents at levels below those producing acute toxicity. However, in New Jersey fluoridating systems conduct their own testing at least once a day and the great majority of people are served by systems that conduct two or more tests each day. The biological significance of the cumulative effect of all routes of exposure is underscored by the Public Health Service (1991) report

of a general increase in incidence of tooth discoloration (fluorosis) due to individual overexposure to fluoride from all sources.

In summary, as an exploratory study that did not include detailed residential and other personal information only obtainable from individual interviews, these results should be interpreted cautiously. From a public health perspective, the findings of this study, even when taken with the overall findings currently in the scientific literature, are not sufficient to recommend that fluoridation of water supplies be halted. The results of this study suggest the advisability of further investigation of possible chronic hazards of fluoride intake from all sources.

It is well known that fluoride provides an important public health benefit by effectively preventing dental caries in children. The Public Health Service (1991) endorses 0.7-1.2 milligrams of fluoride per liter (parts per million) as the optimally beneficial level of for preventing dental caries. However, it is recommended that dentists identify whether children reside in fluoridated communities and appropriately advise on fluoride supplementation.

These conclusions are consistent with the comments of an external review panel from academia and government (Appendix).

CONCLUSIONS AND RECOMMENDATIONS

This exploratory study suggested an association between the fluoridation of drinking water and the incidence of childhood osteosarcoma among males and corroborates the results of a similar type of study conducted nationally by the National Cancer Institute. Since interviews were not conducted in either study, detailed exposure and residency information was not available. Therefore, even taking both studies together, there is insufficient basis to draw conclusions about whether osteosarcoma incidence and fluoridation are causally linked. Furthermore, this study, while more detailed, is based on the small number of cases that occurred during the study years in the fluoridated areas of New Jersey. Because there is definite public health value in the decreased number of dental caries resulting from exposure to the beneficial level of fluoride, additional epidemiologic investigations should be conducted in order to pursue the issue of relative risks and benefits of fluoride ingestion from all sources. In the meantime, the following recommendations are made:

1) Dentists should identify whether individuals reside in fluoridated communities before prescribing fluoride treatments.

2) Use of over-the-counter fluoride supplements, such as fluoride-containing toothpastes, should be re-evaluated with respect to overall fluoride intake.

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TABLE 1 Age-/Sex-Specific Osteosarcoma Incidence in Fluoridated vs Non-fluoridated Municipalities in Seven Counties in the Central New Jersey Study Area, Number of Cases (1979-1987), Population and Average Annual Incidence Rate (Cases Per Million), All Races; NJDOH, 1992.

Sex	Age		Cases	Population	Rates
Males	0-9				
		Fluoridated	2	48,129	4.6
		Non-fluoridated	1	102,123	1.0
	10-19				
		Fluoridated	10	62,990	17.6
		Non-fluoridated	7	151,384	5.1
	20-49				
		Fluoridated	5	141,439	3.9
		Non-fluoridated	5	348,570	1.5
	50-69				
		Fluoridated	0	65,126	0
		Non-fluoridated	7	161,459	4.8
	70+				
		Fluoridated	1	21,614	5.1
		Non-fluoridated	4	48,649	9.1
Females	0-9				
		Fluoridated	0	45,936	0
		Non-fluoridated	2	103,462	2.1
	10-19				
		Fluoridated	3	61,533	5.4
		Non-fluoridated	5	145,790	3.8
	20-49				
		Fluoridated	2	152,173	1.4
		Non-fluoridated	5	362,616	1.5
	50-69				
		Fluoridated	1	76,461	1.4
		Non-fluoridated	2	182,912	1.2
	70+				
		Fluoridated	5	37,634	14.7
		Non-fluoridated	4	77,708	5.7

TABLE 2 Age-/Sex-Specific Osteosarcoma Incidence in Fluoridated vs Non-fluoridated Municipalities in Mercer, Middlesex, and Monmouth Counties, Number of Cases (1979-1987), Population and Average Annual Incidence Rate (Cases Per Million), All Races; NJDOH, 1992.

Sex	Age		Cases	Population	Rates
Males	0-9				
		Fluoridated	2	38,654	5.7
		Non-fluoridated	1	46,708	2.3
	10-19				
		Fluoridated	10	50,297	22.0
		Non-fluoridated	2	67,678	3.2
	20-49				
		Fluoridated	4	115,367	3.8
		Non-fluoridated	2	153,713	1.4
	50-69				
		Fluoridated	0	51,853	0
		Non-fluoridated	2	66,607	3.3
	70+				
		Fluoridated	0	16,930	0
		Non-fluoridated	3	18,478	18.0
Females	0-9				
		Fluoridated	0	36,956	0
		Non-fluoridated	0	44,247	0
	10-19				
		Fluoridated	3	48,976	6.8
		Non-fluoridated	3	65,120	5.1
	20-49				
		Fluoridated	0	122,936	0
		Non-fluoridated	1	157,545	0.7
	50-69				
		Fluoridated	1	60,427	1.8
		Non-fluoridated	1	74,846	1.4
	70+				
		Fluoridated	4	29,068	15.2
		Non-fluoridated	3	28,524	11.6

APPENDIX

CONSENSUS EXTERNAL REVIEW STATEMENT
ON
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May, 1992

With the exceptions noted below, the external review panel generally affirmed that the analysis and conclusions of the draft report were adequate. There were requests for clarifications and suggestions for additional analyses as follows:

Wording

The term "municipalities" should be used throughout, rather than "town" or "township".

The sentence at the top of p. 9 with the phrase, "would tend to keep families within fluoridated or non-fluoridated areas", should read, " suggests that families which move locally would tend to remain in fluoridated areas".

Methods

The three county study area, which encompasses 75% of the fluoridated population in New Jersey, could be expanded to include more of the fluoridated population.

The association of ground water vs surface water sources with osteosarcoma incidence should be examined further since 85% of the fluoridated population in the three county area was supplied by surface water, compared to 30% of the non-fluoridated population. This might be accomplished by adding non-fluoridated municipalities supplied by surface water to the study population or by adding additional counties with fluoridated municipalities that are supplied by ground water sources.

Accurate analysis of the effect of duration and latency of exposure cannot be conducted because individual residential history is not available. However, if the simplifying assumption is made that cases lived their entire lives at the address given at the time of diagnosis, the report could simulate duration/latency data with rough approximation, given the age at diagnosis and the date at which fluoridation was initiated. (Nevertheless, the promoter hypothesis is consistent with shorter latency than an initiation hypothesis.)

The relationship between low pH water with potential higher lead content and the incidence of osteosarcoma should be explored if practicable.

The socioeconomic status (SES) and degree of industrialization of the municipalities in the study area could be added to the analysis (although the SES of individual families in a municipality could vary much more than the relative exposure to drinking water in the municipality).

The results might be fine-tuned by adjusting for population shifts between the 1980 Census and the last year of diagnosis in 1987. This could be accomplished with proportional interpolation using 1990 Census data.

Results

Presentation of results could be usefully separated into the 0-9 and the 10-19 age categories. (Inclusion of ages 20-24 is unnecessary because of the increased potential for in- and out-migration by this age group.)

Conclusions

As stated in the draft, the study is small and municipality-based. Given the methods and results, conclusions are generally appropriate, but it should be further emphasized that, while the risk of osteosarcoma from fluoride exposure is suggested, it is by no means conclusively demonstrated in this analysis. The review panel concurs with the statement in the report that the absence of individually-based data on residential and exposure histories is a major limitation which should be underscored further.

The panel also would like the report to further emphasize the possible multifactorial causality of osteosarcoma other than fluoride exposure and believes that a larger discussion of risk vs benefit would be useful. This discussion could include a statement about the population attributable risk of developing osteosarcoma due to fluoride exposure.

Therefore, only after other, confirmatory, studies could a risk of osteosarcoma from fluoride exposure be conclusively stated. The results of this report alone should not be enough to recommend that fluoridation be halted, but are sufficient to recommend frequent monitoring of artificial fluoride levels in drinking water.

AUTHORS' RESPONSE TO THE CONSENSUS EXTERNAL REVIEW STATEMENT
ON THE DRAFT
"A BRIEF REPORT ON THE ASSOCIATION OF FLUORIDATION OF DRINKING WATER AND THE INCIDENCE OF OSTEOSARCOMA AMONG YOUNG MALES"

August, 1992

In no instance did the panel find major problems with the study. Many of the comments and recommendations were to emphasize points already addressed in the draft, such as the limitations of ecologic studies, or analyses in the process of being added at the time of the review, such as association of surface water vs ground water with osteosarcoma incidence. Below are listed the comments which have already been incorporated in the final report and those which are deferred for future analyses.

I. Completed and Included in Final Report

* Expansion of study to include municipalities in 7 counties
* Effect of duration and latency of exposure, assuming that the residence at the time of diagnosis was the lifetime residence
* Association of ground water and surface water with osteosarcoma incidence
* Separation of the 0-19 age category into 0-9 and 10-19 age categories
* Increased emphasis of the limitations of ecologic studies, the multifactorial causality of osteosarcoma, and the use of only this particular study to set policy
* Inclusion of a population attributable risk calculation
* Uniform use of the wording "municipalities" vs "town" or "township"
* Changing the sentence at the top of page 9 of the draft
* Analysis of the effect of population shifts between 1980 and 1990
* Analysis of the potential association between osteosarcoma incidence and the release of carcinogenic air toxics (from the U.S.E.P.A. Toxic Release Inventory of 1988)

II. Suggestions for Additional Work

* Relationship between low pH water and the incidence of osteosarcoma
* Association of socioeconomic status and degree of industrialization of the municipalities with osteosarcoma incidence

FLUORIDATION AND BONE CANCER

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The NTP (National Toxicology Program) fluoride/cancer study of rats and mice (1) found a statistically significant dose-related increase of osteosarcoma incidence in male rats and, in addition, found fluoride correlations with thyroid follicular cell adenomas, oral and nasal squamous dysplasia, a rare type of liver cancer (hepatocholangiocarcinoma), and, as might have been expected, extensive osteosclerosis. Following this, the Public Health Service, under Dr Hoover *et al*, reviewed the limited SEER epidemiological data which also showed a significant association of water fluoridation with osteosarcoma incidence among males under 20 years of age (2). However, the meaning of this association was questioned by the PHS because of the apparent absence of a linear trend of a putative association over time of which water supplies were fluoridated. Despite this question, it is clear from the data that osteosarcoma in young men had increased over time and that this increase was greater in fluoridated areas. Also, a New York State study, excluding New York City, attempted to analyze its hospital and population data in regard to bone cancer incidence since the 1950s (3). However, due to a change in diagnostic classification from body site (*i.e.*, simply, "bone cancer") to cell type (osteochondroma, Ewing's sarcoma, and osteosarcoma) in the mid-1970s, the true change in incidence of osteosarcoma cannot be calculated. Despite the fact that osteosarcoma is rare (2.9 cases per million people on average annually in New Jersey), it is the most common primary malignant tumor of bone and is one of the principal cancers of childhood. Dr Cohn therefore thought it appropriate to survey its incidence in New Jersey relative to water fluoridation (4).

In his executive summary, Dr Cohn reports his findings of a strong statistical association between water fluoridation and osteosarcoma in young men but points out that the total number of cases is small and that he obtained no data concerning individual residence history, average water ingestion, use of dental fluoride supplements, exposure to other carcinogens, or family cancer history. For these reasons Dr Cohn advises that the results be interpreted cautiously. However, health decisions most often must be made on data which, from the viewpoint of pure science, are in one way or another incomplete. This is inherent in the practice of medicine.

Tables of the study results are reproduced on the following pages.

It should be noted that twelve cases of osteosarcoma were diagnosed among males under 20 in a three county area with the greatest prevalence of fluoridation. Of these, 2 were of age 0-9 and 10 were of age 10-19 years. The rate ratio of incidence in fluoridated *vs* non-fluoridated municipalities in the three county area was 5.1 (95% CI 2.7-9.0)*. Among 10-19 year old males in those three counties, the ratio rate was 6.9 (95% CI 3.3-13). No other age/sex

* CI = Confidence Interval

groups exhibited significant association with fluoride. Thus it can been seen that, for these populations, the chance of osteosarcoma for males age 10-19 years was 6.9 times higher in the fluoridated municipalities.

As noted by Dr Cohn, the etiology of osteosarcoma has not been established. The fact that rapidly growing bone in adolescent males is most susceptible to the development of osteosarcoma suggests that fluoride, which is known to be toxic to bones and a potent enzyme inhibitor, may act as a cancer

Table 1. Age-/sex-specific osteosarcoma incidence in fluoridated vs non-fluoridated municipalities in seven counties in the central New Jersey study area. Number of cases (1979-1987), population and average annual incidence rate (cases per million), all races; NJDOH, 1992.

Sex	Age		Cases	Population	Rates
Males	0-9				
		Fluoridated	2	48,129	4.6
		Non-fluoridated	1	102,123	1.0
	10-19				
		Fluoridated	**10**	**62,990**	**17.6**
		Non-fluoridated	**7**	**151,384**	**5.1**
	20-49				
		Fluoridated	5	141,439	3.9
		Non-fluoridated	5	348,570	1.5
	50-69				
		Fluoridated	0	65,126	0
		Non-fluoridated	7	161,459	4.8
	70+				
		Fluoridated	1	21,614	5.1
		Non-fluoridated	4	48,649	9.1
Females	0-9				
		Fluoridated	0	45,936	0
		Non-fluoridated	2	103,462	2.1
	10-19				
		Fluoridated	3	61,533	5.4
		Non-fluoridated	5	145,790	3.8
	20-49				
		Fluoridated	2	152,173	1.4
		Non-fluoridated	5	362,616	1.5
	50-69				
		Fluoridated	1	76,461	1.4
		Non-fluoridated	2	182,912	1.2
	70+				
		Fluoridated	5	37,634	14.7
		Non-fluoridated	4	77,708	5.7

promoter during this narrow window of susceptibility. Given this, the available SEER epidemiologic data may be more significant than appreciated by the PHS which discounted the observed fluoride/osteosarcoma correlation on the basis of the absence of a linear trend of association with duration of time the water supplies were fluoridated. However, if fluoride acts as a cancer promoter, rather than an initiator, the duration/latency assumption is not warranted.

Table 2. Age-/sex-specific osteosarcoma incidence in fluoridated vs non-fluoridated municipalities in Mercer, Middlesex, and Monmouth Counties. Number of cases (1979-1987), population and average annual incidence rate (cases per million), all races; NJDOH, 1992.

Sex	Age		Cases	Population	Rates
Males	0-9				
		Fluoridated	2	38,654	5.7
		Non-fluoridated	1	46,708	2.3
	10-19				
		Fluoridated	10	50,297	22.0
		Non-fluoridated	2	67,878	3.2
	20-49				
		Fluoridated	4	115,367	3.8
		Non-fluoridated	2	153,713	1.4
	50-69				
		Fluoridated	0	51,853	0
		Non-fluoridated	2	66,607	3.3
	70+				
		Fluoridated	0	16,930	0
		Non-fluoridated	3	18,478	18.0
Females	0-9				
		Fluoridated	0	36,956	0
		Non-fluoridated	0	44,247	..0
	10-19				
		Fluoridated	3	48,976	6.8
		Non-fluoridated	3	65,120	5.1
	20-49				
		Fluoridated	0	122,936	0
		Non-fluoridated	1	157,545	0.7
	50-69				
		Fluoridated	1	60,427	1.8
		Non-fluoridated	1	74,846	1.4
	70+				
		Fluoridated	4	29,068	15.2
		Non-fluoridated	3	28,524	11.8

In the context of the strong correlation of fluoride to osteosarcoma in male rats in the NTP study and the strong epidemiologic evidence of osteosarcoma incidence increase in young male in the US, especially in fluoridated communities, this report from New Jersey adds considerable weight to the probability that fluoride does indeed increase the risk of osteosarcoma among males.

Furthermore, fluoridation/caries studies of the past two decades (5-7), including the latest National Institute of Dental Research study (7), indicate that caries reduction in U.S. schoolchildren is *not* significantly correlated with fluoridation status. Therefore, given that osteosarcoma is potentially fatal and caries is not, and that other documented studies show fluoride-related increases in hip fractures, dental fluorosis, and other health damaging effects, it would be wise to cease all artificial fluoridation. Anyone who chooses to give their children additional fluoride in spite of all these risks would still be free to do so. I can think of no other agent with this degree of risk which is mandated by the PHS to be added to our food or water. The decision to use the agent should be left to the individual and his/her health advisor.

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