ISSN: 0096-9222

# PROCEEDINGS of the PENNSYLVANIA ACADEMY OF SCIENCE

VOLUME 61
Issue No. 2
1987

DANIEL KLEM, JR., Ph.D., EDITOR
DEPARTMENT OF BIOLOGY
MUHLENBERG COLLEGE
ALLENTOWN, PA 18104

63rd ANNUAL MEETING
PENNSYLVANIA ACADEMY OF SCIENCE
12-14 APRIL 1987
AMERICANA HOST CORRAL
LANCASTER, PENNSYLVANIA

*Printed by*

TYPEHOUSE
481 Memorial Parkway
Phillipsburg, NJ 08865
(201) 454-1155

Proceedings of the Pennsylvania Academy of Science 61:138-146: 1987.

1987

# A CURRENT RESTATEMENT AND CONTINUING REAPPRAISAL CONCERNING DEMOGRAPHIC VARIABLES IN AMERICAN TIME-TREND STUDIES ON WATER FLUORIDATION AND HUMAN CANCER[1]

JOHN REMINGTON GRAHAM,[2] DEAN BURK,[3] and PIERRE MORIN[4]

[2]*1100 West Washington Street, Brainerd, MN 56401*

[3]*Dean Burk Foundation, 4719 44th Street, Washington, DC 20016*

*and*

[4]*Centre Local des Services Communautaires, Fortierville, PQ G0S 1JO Canada*

## ABSTRACT

This article reviews an important phase of the debate concerning a striking association between artificial fluoridation of public water supplies and increased crude cancer death rates in large central cities of the United States from 1940 through 1968. The authors believe that this association reveals a causal relationship between water fluoridation and human cancer. Critics insist that the association is explained away by demographic changes in the two groups of central cities which have been compared. The authors evaluate the major papers of these critics, and show that, if all available and pertinent data are standardized by the indirect method for age, race, and sex, the association between fluoridation and cancer remains substantially intact, but somewhat reduced. Attention is also given to a recent suggestion that the association can be explained by changes in population sizes of the twenty cities observed. Analysis of this proposal reveals that, in the cities considered during the period observed, changes in population size were essentially an inverse index of population aging, and yielded adjustments parallel to those for age, race, and sex. It is concluded that artificial fluoridation appears to cause or induce about 20-30 excess cancer deaths for every 100,000 persons exposed per year after about 15-20 years.

## INTRODUCTION

Just over a decade ago, Hon. James Delaney of New York placed into the *Congressional Record* a set of time-trend data showing a striking association between artificial fluoridation of public water supplies and crude cancer death rates (Yiamouyiannis and Burk 1975). Immediate criticism by epidemiologists in the National Cancer Institute of the United States led those who had compiled these data to republish with a partial adjustment by the direct method for age and race (Yiamouyiannis and Burk 1976), then again with a full adjustment by the direct method for age and further consideration for race and sex (Yiamouyiannis and Burk 1977). Additional work has been done setting forth multiple adjustments for age, race, and sex simultaneously by way of the indirect method (Graham and Burk 1984). Certain critics have insisted nevertheless that the observed relationship between water fluoridation and crude cancer death rates is merely an artifact created by demographic fluctuations. This paper will recapitulate and evaluate the data in question, then analyze the claims of those who contend that there is no causal relationship between water fluoridation and human cancer.

## MATERIALS AND METHODS

The basic data consist of a comparison of the average crude or observed cancer death rates for all neoplasms, including leukemias, per 100,000 population per year (CDRs) for two groups of cities, year by year, from 1940 through 1968.

The experimental group consists of the ten largest central cities of the United States, as defined by the 1960 census, which were all fluoridated from 1952 through 1956, each having a crude or observed cancer death rate (CDRo) of more than 155 in 1953. These are Chicago, Philadelphia, Baltimore, Cleveland, Washington, (D.C.), St. Louis, San Francisco, Milwaukee, Pittsburgh, and Buffalo. The dates of fluoridation were determined from *Fluoridation Census 1969,* viz., San Francisco, Baltimore, and Washington in 1952, Pittsburgh in 1952-1953, Milwaukee in 1953, Philadelphia in 1954, St. Louis and Buffalo in 1955, and Chicago and Cleveland in 1956. For this purpose, a city is deemed to have been fluoridated when the fluoride content of its public water supply has been artificially adjusted from its natural level (usually about 0.2 p.p.m.) to a desired level (usually about 1.0 p.p.m.) through the addition of sodium silico fluoride or hydrofluosilicic acid or some such industrial waste product.

The control group consists of the ten largest central cities of the United States, as defined by the 1960 census, which all remained unfluoridated from 1940 through 1968, each having a CDRo of more than 155 in 1953. These are Los Angeles, Boston, New Orleans, Seattle, Cincinnati, Atlanta, Kansas City, Columbus (OH), Newark, and Portland (OR). The year 1968 was taken as the terminus of the observation period, because fluoridation was commenced in Atlanta and Seattle in 1969, then in other control cities in subsequent years.

[1]Received for publication 20 June 1987; reviewed; accepted 23 February 1988.

These CDRs were derived from total cancer deaths for each of the central cities considered as reported in *Vital Statistics of the United States* for every year from 1940 through 1968, and from population figures for each of these cities as reported in *Census of the United States Population* for 1940, 1950, 1960, and 1970, with intercensal population figures being established by linear interpolation. Total cancer deaths for about half of the cities here in question were not available for 1951 and 1952, hence no CDRs were derived for those years. Cancer deaths for Boston in 1953-1954 and 1956-1958 were estimated by linear interpolation.

The aggregate population of the experimental cities was about 11.0 million in 1940, about 11.9 million in 1950, about 11.5 million in 1960, and 10.8 million in 1970. The aggregate population of the control cities was about 5.3 million in 1940, about 6.3 million in 1950, about 7.1 million in 1960, and 7.3 million in 1970.

## RESULTS AND DISCUSSION

Tables 1A and 1B set forth the basic data in terms of the mean CDRo for each group of cities in each year. Table 1A gives unweighted averages, i.e., averages treating each city equally, regardless of population size. The CDRo differences between experimental and control cities in the 1940-50 period are so minuscule that they may be regarded as fortuitous. However, using the years 1953 through 1968 for all values of x and the year-by-year CDRo differences for all values of y, $N = 16$, $df = 14$, $r = +.92$, and $P < .001$, which means that the configuration of those differences was most certainly not a chance happening. Table 1B gives weighted averages, i.e., averages treating each city in proportion to population size. The CDRo differences between experimental and control cities in the 1940-1950 period are so minuscule that they may be regarded as fortuitous. However, using the years 1953 through 1968 for all values of x and the year-by-year CDRo differences for all values of y, $N = 16$, $df = 14$, $r = +.95$, and $P < .001$, which means that the configuration of those differences was most certainly not a chance happening.

Figure 1A pictures the basic data in Table 1A: the ordinate represents CDRo figures, the abscissa represents years from 1940 through 1970, and the two lines perpendicular to the abscissa indicate the period from 1952 through 1956 during which the experimental cities were fluoridated. Figure 1B pictures the basic data in Table 1B: the ordinate, abscissa, and lines perpendicular to the abscissa express the same events as in Figure 1A.

It is apparent that, whether unweighted or weighted averages are considered, essentially the same empirical pattern emerges. A visual examination of Figures 1A and 1B points to three facts: First, from 1940 through 1950, while both groups remained unfluoridated, the observed CDRs for both groups grew in equal and parallel degrees. Secondly, as fluoridation was starting in the experimental group, the observed CDRs in both groups were still similar. And thirdly, from 1953 through 1968, as fluoridation continued in the experimental cities but remained unimplemented in the control cities, the observed CDRs in the experimental group grew noticeably and dramatically faster than the observed CDRs in the control group. These facts must be weighed according to principles of inductive logic, i.e., the second branch of natural reason which adduces generalities and probabilities from observed

TABLE 1A. The basic data in unweighted-average CDRo figures. CDRo = observed cancer death rate. Experimental cities unfluoridated 1940-1950, fluoridated 1953-1968. Control cities unfluoridated 1940-1950 and 1953-1968.

| Year | CDRo Control | CDRo Experimental |
|---|---|---|
| 1940 | 158.4 | 155.5 |
| 1941 | 152.4 | 155.2 |
| 1942 | 153.9 | 157.2 |
| 1943 | 159.2 | 161.6 |
| 1944 | 162.5 | 162.3 |
| 1945 | 165.6 | 168.4 |
| 1946 | 168.5 | 171.6 |
| 1947 | 174.5 | 172.6 |
| 1948 | 178.0 | 173.2 |
| 1949 | 179.5 | 179.4 |
| 1950 | 178.9 | 179.6 |
| 1953 | 188.2 | 191.3 |
| 1954 | 185.6 | 194.1 |
| 1955 | 189.5 | 196.3 |
| 1956 | 189.1 | 203.6 |
| 1957 | 188.4 | 207.1 |
| 1958 | 188.6 | 203.5 |
| 1959 | 193.0 | 204.7 |
| 1960 | 191.1 | 207.0 |
| 1961 | 190.4 | 209.3 |
| 1962 | 190.2 | 207.2 |
| 1963 | 189.4 | 210.9 |
| 1964 | 190.3 | 212.6 |
| 1965 | 194.3 | 218.6 |
| 1966 | 193.4 | 224.8 |
| 1967 | 198.8 | 224.4 |
| 1968 | 199.4 | 226.4 |

TABLE 1B. The basic data in weighted-average CDRo figures. CDRo = observed cancer death rate. Experimental cities unfluoridated 1940-1950, fluoridated 1953-1968. Control cities unfluoridated 1940-1950 and 1953-1968.

| Year | CDRo Control | CDRo Experimental |
|---|---|---|
| 1940 | 159.9 | 155.6 |
| 1941 | 154.5 | 156.3 |
| 1942 | 154.7 | 158.3 |
| 1943 | 159.8 | 162.4 |
| 1944 | 163.2 | 164.2 |
| 1945 | 167.0 | 168.9 |
| 1946 | 169.9 | 171.8 |
| 1947 | 175.0 | 173.9 |
| 1948 | 177.8 | 174.3 |
| 1949 | 180.4 | 181.1 |
| 1950 | 179.0 | 180.8 |
| 1953 | 185.9 | 190.2 |
| 1954 | 182.6 | 192.3 |
| 1955 | 186.1 | 193.9 |
| 1956 | 187.6 | 201.6 |
| 1957 | 185.2 | 204.5 |
| 1958 | 184.3 | 199.7 |
| 1959 | 188.8 | 201.0 |
| 1960 | 185.0 | 205.8 |
| 1961 | 185.7 | 206.0 |
| 1962 | 183.8 | 204.6 |
| 1963 | 184.8 | 208.6 |
| 1964 | 184.8 | 208.7 |
| 1965 | 187.0 | 212.5 |
| 1966 | 188.2 | 218.5 |
| 1967 | 190.1 | 218.4 |
| 1968 | 191.1 | 219.7 |

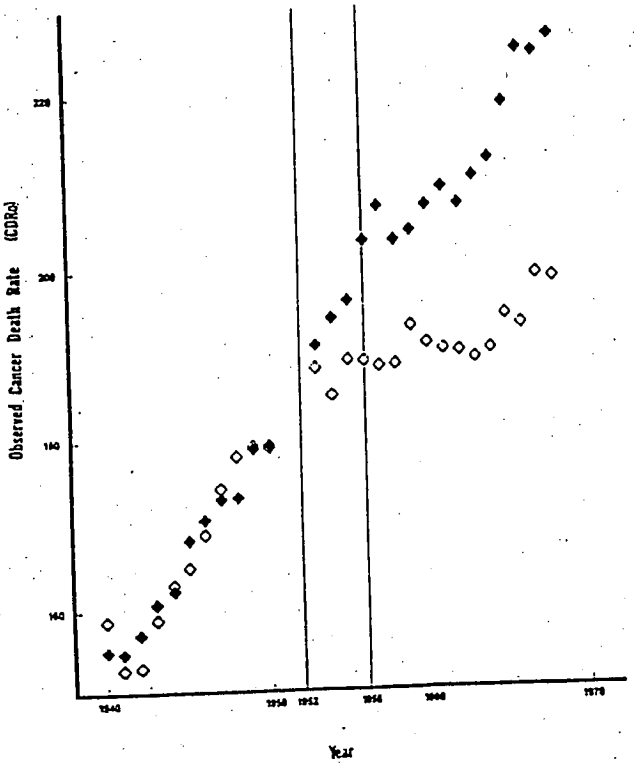


FIGURE 1A. The basic data in unweighted-average CDRo figures. CDRo = observed cancer death rate. Experimental cities unfluoridated 1940-1950, fluoridated 1953-1968. Control cities unfluoridated 1940-1950 and 1953-1968. Solid diamonds represent experimental cities. Open diamonds represent control cities.

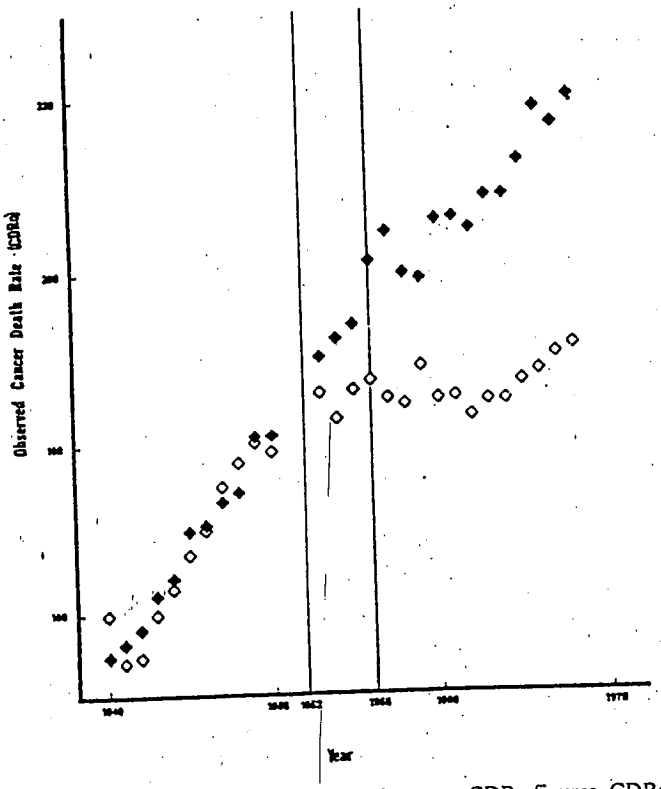


FIGURE 1B. The basic data in weighted-average CDRo figures. CDRo = observed cancer death rate. Experimental cities unfluoridated 1940-1950, fluoridated 1953-1968. Control cities unfluoridated 1940-1950 and 1953-1968.

particulars in space and time.

It is a rule of empirical science, which was first rendered by William of Ockham, that, given a strong association or trend in observed events, the simplest, most obvious and natural explanation should be taken as the cause; and this should be accepted as fact, unless and until the contrary is shown to be more plausible.

Given the trends and association portrayed by Tables 1A and 1B and Figures 1A and 1B, the correct inference, which must stand until the contrary is shown, is that artificial fluoridation of public water supplies produces or aggravates human cancer on a large scale. This conclusion is paralleled by an impressive body of laboratory studies showing that fluoride in water, even at low concentrations, can and does cause the manifestations of cancer and various cancer-related aberrations in organic matter and processes (e.g., Taylor 1954, Herskowitz and Norton 1963, Taylor and Taylor 1965, Chang 1968, Jachimczak et al. 1978, Emsley et al. 1981, Mohamed and Chandler 1982, Imai et al. 1983, Tsutsui and Suzuki et al. 1984a and 1984b, Tsutsui and Ide et al. 1984).

Cancer incidence or mortality in man is influenced by many interacting factors, some tending to reduce, others tending to increase the extent of the disease, including a vast number of environmental, dietary, demographic, socio-economic conditions, practices, and trends. These tend to counteract each other. Good diet may offset aging, quality medical care may neutralize pollution, etc. The principle of Ockham permits us to adduce that, during the period from 1940 through 1950, before introduction of fluoridation in the experimental cities, all environmental, dietary, demographic, socio-economic, and other factors counterbalanced each other so as to make the observed CDRs a true and undistorted index of cancer mortality. The same course of reasoning leads to the conclusion that, during the period from 1953 through 1968, the same interaction continued with respect to all cancer-influencing factors, except for the one known to be new, viz., the introduction and continuation of fluoridation in the experimental cities.

The long base line from 1940 through 1950 thus serves as a presumed control for all known and unknown variables. Sir Francis Bacon or Lord Verulam taught that, without such controls for known and unknown variables, it is difficult if not impossible to adduce the cause of observed phenonmena. If a fluoridated region has an increasing cancer death rate, for example, it cannot be inferred from this alone that fluoridation causes cancer, for something else may account for the trend, such as aging of the population or high consumption of certain carcinogens in solid food. Not until a sufficient quantity of data has been properly organized, as in Tables 1A and 1B, can sound conclusions be drawn. The base line is an epistemological key which permits the inductions, not only that the observed or unadjusted cancer death rates best represent reality, but that fluoridation rather than something else caused the increases in human cancer displayed by the basic data.

Cancer universally strikes the aged much harder than the young, particularly in age groups 45 and over. And it appears that, at least in this country during the second half of the present century, cancer has afflicted nonwhites more than whites, and men more than women. For this reason, it is common in epidemiology to adjust crude CDRs for age, age and sex, age and race, or age, race, and sex. This is particularly important with static comparisons between two geographic areas at a single point in time.

However, the base line in the CDRo data here under consideration serves to control for demographic fluctuations and all other changes which might influence human cancer experience. Thus, we prefer the so-called crude data over adjusted figures as the closest approximation of truth here sought, all things considered.

Yet critics maintain that, among 18 million people in 20 cities over 30 years, it just so happens the experimental cities grew faster in cancer-sensitive segments of their aggregate population, and that this occurred precisely coincident with and proportionate to the commencement and continuation of fluoridation in the experimental cities. Such demographic trends rather than fluoridation might have produced the trends displayed by the basic data. This is possible, but not plausible. It is not what inductive reasoning isolates as likely.

We are not adverse to inquiry as to whether the association indicated by the CDRo figures might not be materially altered by conventional adjustment for age, race, and sex. This process should be pursued, not necessarily to obtain a better view of the facts, but to test the induction from the principle of Ockham that the crude data are not misleading.

The investigation can properly proceed by way of the indirect method of adjusting the weighted averages displayed in Table 1B, provided all pertinent and available data are properly taken into account.

Tables 2A through 2F give the demographic breakdowns for the control and experimental populations in the years 1940, 1950, 1970 expressed in terms of the number of 100,000s of persons in each demographic category as defined by way of age (0–4, 5-14, etc.), race (white and nonwhite), and sex (male and female).

TABLE 2A. Age-race-sex structure* of the control population in 1940.

| Age | White Males | White Females | Non-White Males | Non-White Females |
|---|---|---|---|---|
| 0–4 | 1.418 | 1.372 | 0.208 | 0.206 |
| 5-14 | 3.032 | 2.988 | 0.448 | 0.459 |
| 15-24 | 3.742 | 4.105 | 0.460 | 0.550 |
| 25-34 | 4.026 | 4.340 | 0.516 | 0.601 |
| 35–44 | 3.675 | 3.838 | 0.491 | 0.536 |
| 45-54 | 3.243 | 3.311 | 0.351 | 0.333 |
| 55-64 | 2.228 | 2.412 | 0.187 | 0.173 |
| 65-74 | 1.215 | 1.435 | 0.088 | 0.095 |
| 75-84 | 0.402 | 0.563 | 0.019 | 0.026 |
| 85+ | 0.056 | 0.094 | 0.005 | 0.008 |

Total: $53.225 \times 10^5$

*All figures given in 100,000s. Figures for 75-84 and 85+ estimated from 75+ census data, and known national trends in 1940; that is 12.2 percent for white males 75 and older, 14.3 percent for white females 75 and older, 19.5 percent for non-white males 75 and older, and 23.6 percent for non-white females 75 and older were respectively 85 and older.

TABLE 2B. Age-race-sex structure* of the experimental population in 1940.

| Age | White Males | White Females | Non-White Males | Non-White Females |
|---|---|---|---|---|
| 0–4 | 3.045 | 2.937 | 0.446 | 0.446 |
| 5-14 | 6.655 | 6.476 | 0.956 | 0.983 |
| 15-24 | 8.269 | 8.781 | 0.902 | 1.086 |
| 25-34 | 8.459 | 9.031 | 1.053 | 1.161 |
| 35–44 | 7.598 | 7.735 | 1.074 | 1.060 |
| 45-54 | 7.057 | 6.791 | 0.789 | 0.698 |
| 55-64 | 4.426 | 4.379 | 0.372 | 0.342 |
| 65-74 | 2.218 | 2.593 | 0.171 | 0.194 |
| 75-84 | 0.663 | 0.897 | 0.036 | 0.050 |
| 85+ | 0.092 | 0.150 | 0.009 | 0.016 |

Total: $110.101 \times 10^5$

*All figures given in 100,000s; see footnote Table 2A.

TABLE 2C. Age-race-sex structure* of the control population in 1950.

| Age | White Males | White Females | Non-White Males | Non-White Females |
|---|---|---|---|---|
| 0–4 | 2.486 | 2.396 | 0.467 | 0.460 |
| 5-14 | 3.334 | 3.264 | 0.621 | 0.631 |
| 15-24 | 3.502 | 3.824 | 0.572 | 0.697 |
| 25-34 | 4.398 | 4.651 | 0.759 | 0.872 |
| 35-44 | 3.958 | 4.299 | 0.695 | 0.748 |
| 45-54 | 3.466 | 3.720 | 0.516 | 0.515 |
| 55-64 | 2.735 | 3.002 | 0.282 | 0.277 |
| 65-74 | 1.612 | 2.040 | 0.159 | 0.178 |
| 75-84 | 0.560 | 0.848 | 0.043 | 0.052 |
| 85+ | 0.086 | 0.158 | 0.007 | 0.012 |

Total: $62.901 \times 10^5$

*All figures given in 100,000s.

TABLE 2D. Age-race-sex structure* of the experimental population in 1950.

| Age | White Males | White Females | Non-White Males | Non-White Females |
|---|---|---|---|---|
| 0–4 | 4.457 | 4.279 | 1.047 | 1.042 |
| 5-14 | 6.199 | 6.062 | 1.420 | 1.451 |
| 15-24 | 6.521 | 6.972 | 1.302 | 1.593 |
| 25-34 | 8.179 | 8.671 | 1.744 | 2.031 |
| 35-44 | 7.386 | 7.966 | 1.559 | 1.669 |
| 45-54 | 6.511 | 6.820 | 1.215 | 1.137 |
| 55-64 | 5.405 | 5.471 | 0.631 | 0.584 |
| 65-74 | 2.865 | 3.298 | 0.302 | 0.337 |
| 75-84 | 0.896 | 1.274 | 0.079 | 0.101 |
| 85+ | 0.124 | 0.226 | 0.013 | 0.022 |

Total: $118.858 \times 10^5$

*All figures given in 100,000s.

TABLE 2E. Age-race-sex structure* of the control population in 1970.

| Age | White Males | White Females | Non-White Males | Non-White Females |
|---|---|---|---|---|
| 0–4 | 2.005 | 1.914 | 1.056 | 1.053 |
| 5-14 | 4.278 | 4.129 | 2.236 | 2.238 |
| 15-24 | 4.729 | 5.158 | 1.608 | 1.917 |
| 25-34 | 3.557 | 3.415 | 1.247 | 1.462 |
| 35-44 | 2.891 | 2.930 | 1.007 | 1.200 |
| 45-54 | 3.096 | 3.457 | 0.859 | 1.001 |
| 55-64 | 2.591 | 3.123 | 0.611 | 0.716 |
| 65-74 | 1.622 | 2.437 | 0.354 | 0.511 |
| 75-84 | 0.756 | 1.389 | 0.122 | 0.179 |
| 85+ | 0.173 | 0.365 | 0.034 | 0.054 |

Total: $73.477 \times 10^5$

*All figures given in 100,000s.

TABLE 2F. Age-race-sex structure* of the experimental population in 1970.

| Age | White Males | White Females | Non-White Males | Non-White Females |
|---|---|---|---|---|
| 0–4 | 2.413 | 2.313 | 2.002 | 1.995 |
| 5-14 | 5.165 | 4.992 | 4.557 | 4.584 |
| 15-24 | 5.470 | 5.954 | 3.163 | 3.775 |
| 25-34 | 4.196 | 4.037 | 2.279 | 2.812 |
| 35-44 | 3.477 | 3.512 | 2.071 | 2.512 |
| 45-54 | 4.094 | 4.710 | 1.832 | 2.090 |
| 55-64 | 3.908 | 4.738 | 1.263 | 1.441 |
| 65-74 | 2.512 | 3.622 | 0.748 | 0.900 |
| 75-84 | 1.176 | 1.963 | 0.238 | 0.329 |
| 85+ | 0.225 | 0.442 | 0.059 | 0.096 |

Total: $107.666 \times 10^5$

*All figures given in 100,000s.

TABLE 3. The standard population: known cancer death rates in each of the forty age-race-sex categories for the United States in 1940.

| Age | White Males | White Females | Non-White Males | Non-White Females |
|---|---|---|---|---|
| 0-4 | 5.2 | 4.6 | 2.1 | 3.1 |
| 5-14 | 3.2 | 3.1 | 1.9 | 1.6 |
| 15-24 | 6.3 | 4.5 | 4.3 | 6.3 |
| 25-34 | 11.9 | 20.5 | 11.6 | 39.4 |
| 35-44 | 38.3 | 78.3 | 47.0 | 122.4 |
| 45-54 | 133.3 | 198.3 | 156.4 | 267.2 |
| 55-64 | 357.1 | 385.4 | 291.9 | 376.6 |
| 65-74 | 759.5 | 677.1 | 445.0 | 486.1 |
| 75-84 | 1320.3 | 1080.5 | 532.2 | 473.7 |
| 85+ | 1569.9 | 1384.5 | 499.1 | 608.2 |

Table 3 represents the known cancer death rates per 100,000 in each of the corresponding demographic categories for the United States in 1940. This is the standard population which has been used to calculate the so-called "expected" cancer death rate (CDRe) for the control group of cities, and for the experimental group of cities, first for 1940, then for 1950, then for 1970.

The United States in 1940 has been selected as the standard population, not arbitrarily, but purposefully. A standard population should consist of a set of rates which will give what may be fairly expected for each observed population, in light of its demographic composition, and in the absence of factors tending to make its cancer experience abnormally high or low. Such a set of rates would presumably be what existed across the country when the observations began. Thus, the right standard for twenty large American cities from 1940 through 1950 and from 1953 through 1968 would be the United States in 1940.

It is needful, first, to derive a set of CDRe figures for the control and experimental groups in 1940, 1950, and 1970, multiplying the figures in each of the Tables 2A through 2F by the rates in Table 3, thus deriving expected cancer deaths which are then added up for both groups in each of the years in question, then divided by the population totals given in Tables 2A through 2F, leaving resulting fractions which are finally reduced to a common denominator of 100,000.

Next, these CDRe figures, once derived, must be paired with their corresponding CDRo figures. It is incorrect to take the CDRo figures merely as reported for the years 1940, 1950, and 1970. The data for the years 1953 through 1968 are those which cause all the concern. If only censal data are used, the period from 1950 through 1970 will be characterized by CDRo data for two years only, one before, the other after the observation period of 1953 through 1968, and every particle of information concerning such observation period will be left out altogether.

For this reason, it is preferable to do a linear-regression analysis of the CDRo data for the control, then the experimental cities, for the observation period of 1953 through 1968. The regression lines can then be extended to 1950 and 1970 for both the control and experimental cities, so as to give us putative CDRo figures for those years, figures which represent the actual trends of the critical time span.

Similarly, a linear-regression analysis should be done of the CDRo data for the control, then the experimental cities for the base-line period of 1940 through 1950. Where the regression lines intersect the axes for 1950 and 1970, the putative CDRo figures for those years will be established.

Thus, we shall have regression lines establishing, first for control cities, then experimental cities CDRo values for 1940 and 1950, and also 1950 and 1970. The control and experimental CDRe values for 1940, 1950, and 1970 must be paired with these CDRo values.

TABLE 4. Age-race-sex adjustment of the basic data for 1940-1950 and 1950-1970. CDRo = observed cancer death rate. CDRe = expected cancer death rate. See text for details of calculation. Experimental cities unfluoridated 1940-1950, fluoridated 1953-1968. Control cities unfluoridated 1940-1950 and 1953-1968.

| | Experimental Cities | | | |
|---|---|---|---|---|
| | 1940 | 1950 | 1950 | 1970 |
| CDRo | 154.2 | 181.8 | 186.3 | 222.6 |
| CDRe | 123.2 | 141.2 | 141.2 | 165.9 |
| CDRo/CDRe | 1.252 | 1.288 | 1.319 | 1.342 |
| CDRo - CDRe | 31.0 | 40.6 | 45.1 | 56.7 |
| | Control Cities | | | |
| | 1940 | 1950 | 1950 | 1970 |
| CDRo | 153.5 | 181.3 | 183.6 | 188.8 |
| CDRe | 135.7 | 150.5 | 150.5 | 159.1 |
| CDRo/CDRe | 1.131 | 1.205 | 1.220 | 1.187 |
| CDRo - CDRe | 17.8 | 30.8 | 33.1 | 29.7 |

Table 4 gives a full set of figures for the adjustment, as derived from Tables 1B, 2A through 2F, and 3, and linear-regression analysis of observed CDRs, including two distinct indices of adjustment, viz., the ratio, CDRo/CDRe, and the difference, CDRo−CDRe, for the control cities, then for the experimental cities, in 1940 and 1950, and again for 1950 and 1970.

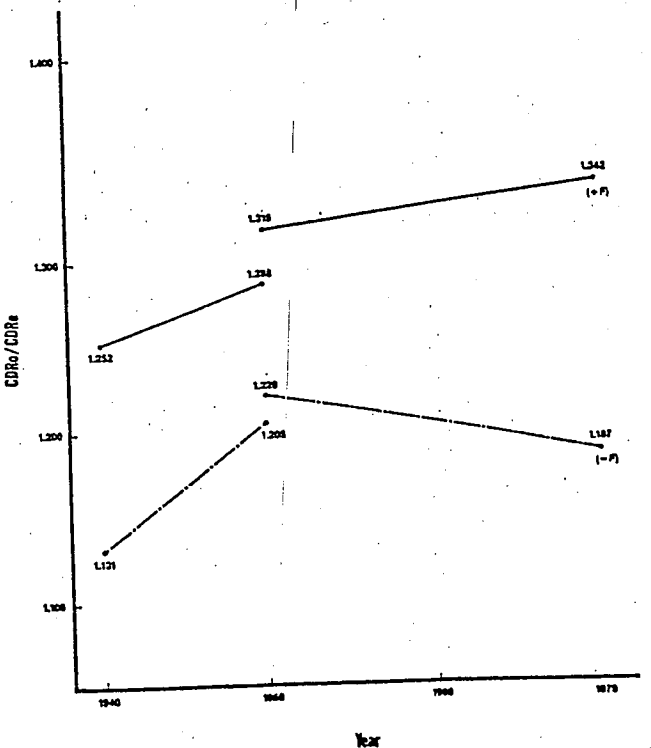


FIGURE 2A. Age-race-sex adjustment of the basic data for 1940-1950 and 1950-1970 in terms of CDRO/CDRe. See Table 4. Solid lines represent experimental cities, unfluoridated 1940-1950, fluoridated 1953-1968. Broken lines represent control cities, unfluoridated 1940-1950 and 1953-1968.

Figures 2A and 2B picture the patterns of the adjusted data. In Figure 2A the ordinate represents CDRo/CDRe, while in Figure 2B the ordinate represents CDRo−CDRe, and in both diagrams the abscissa represents years from 1940 through 1970. These show visually why it is important to add the adjusted trends of 1940-1950 period to those of the 1950-1970 period so as to achieve a cumulative adjusted effect. The commencement of fluoridation in the experimental cities was accompanied by, not one, but two

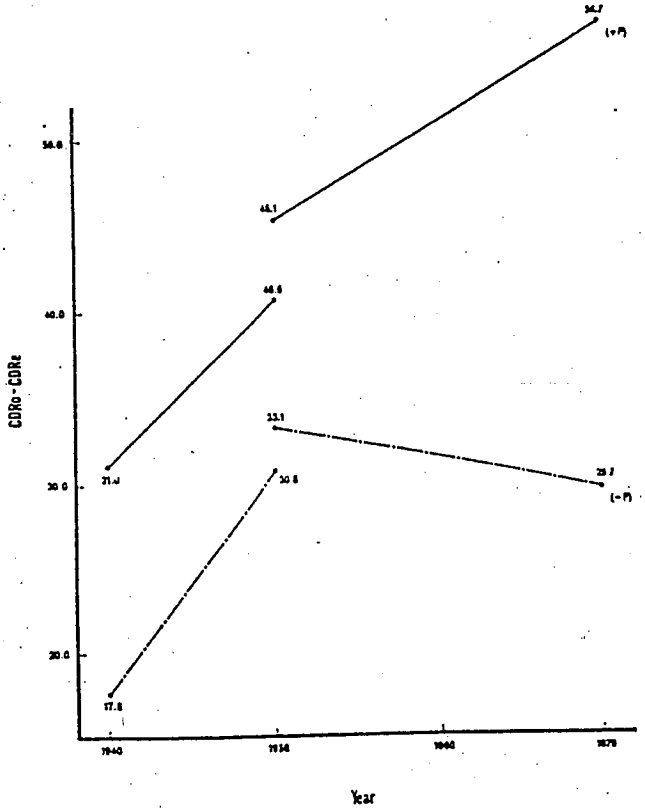


FIGURE 2B. Age-race-sex adjustment of the basic data for 1940-1950 and 1950-1970 in terms of CDRo – CDRe. See Table 4. Solid lines represent experimental cities, unfluoridated 1940-1950, fluoridated 1953-1968. Broken lines represent control cities, unfluoridated 1940-1950 and 1953-1968.

changes in adjusted figures: one was a change in post-1950 trends, the other was a change from pre-1950 trends, and both changes should be accounted for; putting it less abstractly and more spacially, the pre-1950 lines can be squeezed together, and this will widen the net distance between the post-1950 lines at all points.

Drawing from Table 4, the time-dependent increase in CDRo associated with fluoridation is 31.3 = [(222.6 – 188.8) – (186.3 – 183.6)] + [(154.2 – 153.5) – (181.8 – 181.3)]. That is to say, considering the cumulative effect of the time spans both before and after 1950, but acknowledging the difference in the lengths of such time spans, the introduction of fluoridation in the experimental cities during the 1952-1956 period is associated with an observed increase in the cancer death rate of 31.3 cancer deaths per 100,000 persons exposed over 15 to 20 years.

Again drawing from Table 4, the time-dependent increase in CDRo - CDRe associated with fluoridation is 18.4 = [(56.7 - 29.7) - (45.7 - 33.1)] + [(31.0 - 17.8) - (40.6 - 30.8)]. That is to say, considering the cumulative effect of the time spans before and after 1950, but acknowledging the difference in the lengths of such time spans, the introduction of fluoridation during the 1952-1956 period is associated with an adjusted increase in the death rate of 18.4 cancer deaths per 100,000 persons exposed after 15 to 20 years. The same adjusted increase, as expressed in terms of the less informative index, i.e., the ratio, CDRo/CDRe, is +.094.

Once more drawing from Table 4, the time-independent increase in CDRo - CDRe associated with fluoridation is 69.2% of the time-independent increase in CDRo associated with fluoridation, inasmuch as {[(31.0 - 17.8) - (40.6—30.8)]/10 + [(56.7 - 29.7) - (45.1 - 33.1)]/20} / {[(154.2 - 153.5) - (181.8 - 181.3)]/10 + [(222.6 - 188.8) – (186.3 - 183.6)]/20} = 21.8/31.5 = 0.692. That is to say, considering the cumulative effect of the time spans before and after 1950, but disregarding the difference in the lengths of the time spans before and after 1950 so as to consider the problem in terms of equivalent units of time for the sake of comparison, then it can be said that at least 69.2% of whatever increase in CDRo is associated with fluoridation cannot be attributed to fluctuations in the age-race-sex compositions of the control and experimental populations.

Whether age-race-sex adjustment in this instance should be time-dependent or time-independent is largely a matter of conceptual or philosophical preference.

In any event, the natural conclusion from these statistical manipulations is that particularly changes in age structure, and to a lesser extent changes in race and sex composition of the control and experimental populations over time, account for part of the increase in cancer mortality associated with fluoridation, even though the greater proportion thereof cannot be so explained. This adjustment must be taken with caution, because the demographic changes thereby measured could be and presumably are counterbalanced to some extent by environmental, dietary, socio-economic, and other factors so as to leave the crude CDRs, as we believe, the best portrayal of reality when all is said and done. Depending on whether crude or adjusted figures are preferred, the fairest quantification of fluoridation-caused cancer appears to be about 20 to 30 excess cancer deaths per 100,000 persons exposed per year after 15 to 20 years.

Notwithstanding what has just been set forth, it has been asserted over and again by defenders of water fluoridation that indirect-method adjustment of the basic data for age, race, and sex eliminates the observed differences in crude CDRs between the fluoridated and unfluoridated cities after 1950 (Oldham and Newell 1977, Doll and Kinlen 1977, Kinlen and Doll 1981, Chilvers 1983, and Knox 1985).

These critics have advocated adjustment of weighted averages, as given in Tables 1B, through the use of ten-city demographic breakdowns as in Tables 2A through 2F, and nationwide standard populations, as illustrated in Table 3.

The main point of disagreement is that, whereas we have derived putative CDRo figures by linear-regression analysis of all available and pertinent data, i.e., the crude CDRs characterizing the observation period of 1953 through 1968, the investigators just mentioned have taken reported or pericensal CDRo figures for 1950 and 1970. If, as they say, only the censal or pericensal data for 1950 and 1970 ought to be taken into account, the association between fluoridation and cancer is wiped away by adjustment. If instead, as we insist, the intermediate data for 1953 through 1968 must be used, a large association remains, notwithstanding adjustment.

A crude CDR is a reduced fraction based on the number of cancer deaths for the numerator, and the population size for the denominator. Year-by-year cancer deaths are usually known in both census and intercensal years. In census years, the actual size of a population is known. For intercensal years, however, population sizes must be estimated. In the United States, for legal and practical reasons, a census is taken only once each decade, as in 1940, 1950, etc. The procedure used for estimation of intercensal population sizes, known as linear interpolation, assumes that, if the population of a certain area increases or decreases between two census years, say 1950 and 1960, such increase or decrease occurs in equal steps for each intercensal year: hence an estimated population size in 1951 is reckoned as the population size in 1950 plus (or minus, as the case may be) 10% of the difference between the population size in 1960 and the population size in 1950, the population size in 1952 is reckoned by adding (or substracting, as the case may be) 20% of such difference, and so on.

Linear interpolation is founded on the principle of Ockham, and so is generally sound in point of inductive logic: if, for example, the population size of a given area is 100,000 in, say, 1940, and 120,000 ten years later in 1950, the simplest, most obvious and natural explanation is that the population size grew by about 2,000 during each of the intervening years, and such explanation must be assumed unless and until the contrary is shown.

There are, of course, situations in which population sizes are known to change unevenly, as where a municipality rapidly increases then rapidly decreases in population size within a few years in consequence of a short-term boom and bust in the local economy. But changes such as these are abnormal, for which reason linear interpolation is ordinarily regarded as safe, and is routinely followed as a standard practice for estimation of intercensal population sizes and cancer death rates in modern applied epidemiology (e.g., Hilleboe et al. 1956, and H.E.W. 1974).

The basic data set forth in Tables 1A and 1B consist mostly of intercensal CDRo figures which are based on interpolated estimates of population sizes. These estimates assume that, among millions of people in each of two groups of large cities spread out over the face of a great continent, notwithstanding the possibility of some uneven changes in certain localities from time to time, increases or decreases will in the end average out into fairly equal steps between census years. It is unreasonable in the context of the data here considered to postulate the contrary.

Chilvers (1983) claims that Washington, D.C., in the experimental group did not grow linearly between 1940 and 1950, between 1950 and 1960, and between 1960 and 1070, but does not show what these non-linear changes would produce a material variation from the average CDRo figures given in Tables 1A and 1B. It is sufficient to say that some uneven fluctuations in the number of people living within any major city over thirty years may be expected, since all human activity, including birth, death, in-migration, and out-migration, is spontaneous in some degree, yet overall, when large enough numbers are involved, such as we have here, distinctive trends can be anticipated, and these can be fairly approximated.

Epidemiology cannot proceed without inductive inferences based on reasonable assumptions which yield sound estimates. The selection of a standard population for calculation of CDRe figures is founded on judgment fully as intuitive as the decision to estimate intercensal CDRo figures by linear interpolation. Both judgments are equally conventional in practice, equally necessary in theory, and equally important in effect (cf. Graham and Burk 1984).

The decision to use intercensal CDRs is a matter of pre-mathematical judgment. Once those data are established as facts by pure logic, it is statistically obligatory to use all CDRs in each group from 1953-1968, and statistically incorrect to use only censal or pericensal figures for 1950 and 1970, when seeking to define the trends of crude CDRs in the control and experimental cities after 1950.

A recent and important paper suggests that any apparent association between fluoridation and cancer might be explained by changes in population sizes (Burgstahler et al. 1986). These investigators considered crude pericensal CDRs for 1940, 1950, 1960, 1970, and 1980 in each of the 40 largest central cities of the United States with a population of at least 25,000 in 1950 and at least 100,000 in 1980. They report indifferent or inconsistent CDRo responses to fluoridation where commenced and continued, but generally inverse CDRo responses to changes in population size.

We do not doubt that, at least in large central cities of the United States during the 20th Century, changes in population size are an inverse index or another dimension of population aging, i.e., that decreases in population size tend to be characterized by out-migration of younger people, lower birth rates, faster population aging, and more cancer than otherwise would be found, while increases in population size tend to be characterized by in-migration of younger people, higher birth rates, slowing or reversal of population aging, and less cancer than would otherwise be found. Nor do we doubt that, generally speaking, population aging has a greater influence on crude CDRs than any one environmental factor, including fluoridation.

In light of these concessions, we think the findings of Burgstahler et al. (1986) are quite understandable in themselves, nor do we take issue with them, yet we believe they are not incompatible with the association between fluoridation and cancer which we have found.

We think the implications of these findings should be considered in relation to the data displayed in Tables 1A and 1B.

Among the cities represented by the data in Tables 1A and 1B from 1940 through 1950, the rate of population growth in the control group was proportionately faster than in the experimental group, the age-adjusted CDR (i.e., CDRo - CDRe) grew relatively faster in the control group than in the experimental group, while the crude CDR (i.e., CDRo) grew equally in both groups. This is consistent with and confirmatory of the assumption that changes in population size are an inverse index or another dimension of population aging, for, if true, a faster increase in population size, as occurred in the control cities before 1950, will tend to be accompanied by slower aging, as happened in the control cities during the same period, and that in turn will be likely to produce a faster growth in the age-adjusted CDR than in the crude CDR, as, again, was evident in the control cities at the same time.

After 1950 the experimental cities became smaller in population but aged faster, while the control cities grew larger in population and aged hardly at all. This further supports the notion of an inverse relationship between changes in population size and population aging, a relationship which would help explain why, after 1950, the age-adjusted CDR difference between the experimental and control groups was less than the observed CDR difference.

In quantifying the impact of changes in the population sizes of the various cities represented by the basic data set forth in Tables 1A and 1B, we have been compelled to use a method which confines all attention within the range of the 1950-1070 epoch. But, if such measurement of the impact of changes in population size compares closely with age-race-sex adjustment for the 1950-1970 period, then it is safe enough to conclude that, at least in regard to the basic data here considered, changes in population size are an inverse index of population aging, and that the total impact of changes in population size from 1940 through 1970 is about the same as the total impact of age-race-sex fluctuations over the same time span.

Initially, we note from Table 4 that, if only the 1950-1970 epoch is considered, and the 1940-1950 period is entirely disregarded, the increase in CDRo associated with fluoridation is 31.1 = (222.6 - 188.8) - (186.3 - 183.6), while the increase in CDRo - CDRe is 15.0 = (56.7 - 29.7) - (45.1 - 33.1). The age-race-sex adjustment cuts the observed figure in the post-1950 by 51.8% or about half.

In considering changes in population size during the post-1950 period, we have compiled three kinds of data from sources already listed, and the particulars of our compilation are displayed in Table 5:

TABLE 5. Data used in adjustment for changes in population size, 1950-1970. %+F = percentage of the span fluoridated. %ΔP = percentage change in the population size. %ΔCDRo = percentage change in observed cancer death rate. See text for details in calculation.

| Cities | %+F | %Δp | %ΔCDRo |
|---|---|---|---|
| Experimental | | | |
| Chicago | 75 | −7.0 | +13.8 |
| Philadelphia | 85 | −5.9 | +16.3 |
| Baltimore | 95 | −4.6 | +23.2 |
| Cleveland | 75 | −17.9 | +29.6 |
| Washington | 95 | −5.6 | +18.6 |
| St. Louis | 80 | −27.4 | +25.4 |
| San Francisco | 95 | −7.6 | +26.4 |
| Milwaukee | 90 | +12.6 | +2.8 |
| Pittsburgh | 90 | −23.2 | +37.4 |
| Buffalo | 80 | −20.2 | +29.8 |
| Control | | | |
| Los Angeles | 0 | +42.9 | 0.0 |
| Boston | 0 | −20.0 | +1.8 |
| New Orleans | 0 | +4.2 | +24.2 |
| Seattle | 10 | +11.9 | −3.8 |
| Cincinnati | 0 | −10.1 | +22.6 |
| Atlanta | 10 | +50.2 | +12.3 |
| Kansas City | 0 | +10.9 | +13.7 |
| Columbus | 0 | +43.6 | −8.8 |
| Newark | 0 | −13.0 | −9.4 |
| Portland | 0 | +2.4 | +21.7 |

—%+F, i.e., the percentage of the 20-year span after 1950 through 1970 during which each city was fluoridated. Thus, e.g., 75 is assigned to Chicago, because that city began fluoridation in 1956, and so was fluoridated about 75% of the 20-year period;

—%Δp, i.e., the percentage change in the population size of each city after 1950 through 1970. Thus, e.g., −7.0 is assigned to Chicago, because the population of that city in 1970 was 7% less than its population in 1950;

—%ΔCDRo, i.e., the percentage change in CDRo for each city between 1950 and 1970. For this purpose we considered the CDRo data for each city from 1953 through 1968, then extrapolated to 1950 and 1970 by linear regression. Thus, e.g., +13.8 is assigned to Chicago, because there the CDRo in 1970 was 13.8% higher than the CDRo in 1950.

We then proceeded to correlate these various factors for all twenty cities to determine their relationships to each other:

—Using %+F for all values of x and %ΔCDRo for all values of y, $N = 20$, $df = 18$, $r = +.55$, and $P < .02$. This means that the presence of fluoridation during the 1950-1970 period anywhere among the twenty cities gave rise to a moderate but real likelihood that CDRo would increase.

—Using %Δp for all values of x and %ΔCDRo for all values of y, $N = 20$, $df = 18$, $r = -.54$, and $P < .02$. This means that a decrease in population size anywhere among the twenty cities during the 1950-1970 period gave rise to a moderate but real likelihood that CDRo would increase, and that an increase in population size give rise to a moderate but real likelihood that CDRo would decrease.

The magnitude of the positive correlation coefficient ($r = +0.55$) measuring the direct relationship between fluoridation and changes in CDRo is virtually equal to the magnitude of the negative correlation coefficient ($r = -0.54$) measuring the inverse relationship between changes in population size and changes in CDRo. Therefore, if, among the twenty cities during the post-1950 period, whenever and wherever fluoridation was present, there was a corresponding and proportionate decrease in population size, etc.—if, in other words, the correlation coefficient measuring the relationship between fluoridation and changes in population size came very close to or equalled −1.00—, then the apparent association between fluoridation and cancer among the twenty cities would be an artifact of demographic fluctuations, viz., changes in population size.

—Using %+F for all values of x and %Δp for all values of y, $N = 20$, $df = 18$, $r = -0.48$, and $P < 0.04$. This means that, whenever and wherever fluoridation was implemented, there was a corresponding decrease in population size only to the extent of $47.1\% = 0.471 = -0.48/(0.55/-0.54)$, and that, whenever and wherever fluoridation was not implemented, there was a corresponding increase in population size only to the extent of 47.1%.

The adjustment for changes in population size, like the adjustment for fluctuations in age-race-sex composition, cuts the crude figures in the post-1950 period by about half. These two demographic adjustments of CDRo data appear to be two sides of the same coin.

Therefore, demographic variables leave essentially unimpaired the substantial association and presumed causal relationship between fluoridation and cancer. It remains fair enough, all things considered, to expect 20 to 30 more cancer deaths per 100,000 persons exposed per year, within 15 to 20 years after fluoridation has been introduced, than otherwise would have occurred.

In light of this conclusion, we urge the governments of civilized countries of the world to bring about a prompt end to artificial fluoridation of public water supplies.

## LITERATURE CITED


Burgstahler, A., D. DeFries, and M. Shelton. 1986. Cancer Mortality in Relation to Fluoridation and Population Changes, presented to the 15th Conference of the International Society for Fluoride Research, Utah State University, Logan, UT.

Chang, C. 1968. Effect of Fluoride on Nucleotides and Ribonucleic Acid in Corn Seedling Roots, Plant Physiol. 43:669.

Chilvers, C. 1983. Cancer Mortality and Fluoridation of Water Supplies in 35 Cities, Int. Jour. Epid. 12:397.

Doll, R., and L. Kinlen. 1977. Fluoridation of Water and Cancer Mortality in the U.S.A., Lancet, June 18, 1977: 1300.

Emsley, J., D. Jones, J. Miller, R. Overill, and R. Waddilove. 1981. An Unexpectedly Strong Hydrogen Bond: Ab Initio Calculations and Spectroscopic Studies of Amide-Fluoride Systems, Jour. Am. Chem. Soc. 103:24.

Graham, J., and D. Burk. 1984. Lord Jauncey and Justice Flaherty: Opposing Views of the Fluoridation-Cancer Link, Fluoride 17:63.

Herskowitz, I., and I. Norton. 1963. Increased Incidence of Melanotic Tumors in Two Strains of Drosophila Melanogaster, Genetics 48:307.

U.S. Dept. H.E.W.. 1974. U.S. Cancer Mortality by County: 1950-1969, N.I.H. Pub. No. 74-615.

Hilleboe, M., E. Schlesinger, H. Chase, K. Cantwell, D. Ast, D. Smith, B. Wachs, D. Overton, and H. Hodge. 1956. Newburgh-Kingston Caries-Fluorine Study: Final Report, Jour. Am. Dent. Assoc. 52:290 at 304 and 306.

Imai, T., M. Niwa and M. Ueda. 1983. Effects of Fluoride on Cell Growth of Two Human Cell Lines and on DNA and Protein

Synthesis in HeLa Cells, Acta Pharm. Tox. 52:8.

Jackimczak, D., and B. Skotarczak. 1978. The Effect of Fluoride and Lead Ions on Human Leukocytes in Vitro, Gen. Pol. 19:353.

Kinlen, L., and R. Doll. 1981. Fluoridation of Water Supplies and Cancer Mortality: a Reexamination of Cancer Mortality in Cities of the U.S.A., Jour. Epid. Com. H. 35:239.

Knox, E. 1985. Fluoridation of Water and Cancer: A Review of the Epidemiological Evidence, H.M. Stationary Office, London.

Mohamed, A., and M. Chandler. 1982. Cytological Effects of Sodium Fluoride on Mice, Fluoride 15:110.

Oldham, P., and D. Newell. 1977. Fluoridation of Water and Cancer Mortality—a Possible Association, Appl.Stat. 26:125.

Taylor, A. 1954. Sodium Fluoride in the Drinking Water of Mice, Dent. Dig. 60:170.

Taylor, A., and N. Taylor. 1963. Effect of Sodium Fluoride on Tumor Growth, Proc. Soc. Exptl. Biol. Med. 119:252.

Tsutsui, T., K. Ide, and H. Maizumi. 1984. Induction of Unscheduled DNA Synthesis in Cultured Human Oral Keratinocytes by Sodium Fluoride, Mut. Res. 140:43.

Tsutsui, T., N. Suzuki, and M. Ohmori. 1984a. Sodium Fluoride-Indiced Morphological and Neoplasic Transformation, Chromosome Exchanges, and Unscheduled DNA Synthesis in Cultured Syrian Hamster Embryo Cells, Cancer Res. 44:938.

Tsutsui, T., N. Suzuki, M. Ohmori, and H. Maizumi. 1984b. Cytotoxity, Chromosome Aberrations and Unschedules DNA Synthesis in Cultured Human Diploid Fibroblasts Induced by Sodium Fluoride, Mut. Res. 139:193.

Yiamouyiannis, J., and D. Burk. 1975. Cancer From Our Drinking Water?, Cong. Rec., Dec. 16, 1975, p. H12731.

Yiamouyiannis, J., and D. Burk. 1976. Fluoridation of Public Water Systems and Cancer Death Rates, Am. Soc. Biol. Chem., Fed. Proc. 35:1707.

Yiamouyiannis, J., and D. Burk. 1977. Fluoridation and Cancer: Age-Dependence of Cancer Mortality Related to Artificial Fluoridation, Fluoride 10:102.