Fluoridation of Water and Cancer: A Review of the Epidemiological Evidence

Report of the Working Party

Chairman: Professor E G Knox

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PREFACE

There is ample evidence, from many places and over many years, that fluoridation of the public water supply leads to a substantial reduction in dental caries, with all that means in prevention of suffering, inconvenience and unnecessary cost. It can be shown that the beneficial effect of fluoride is significant, whatever other measures are taken in relation to sound nutrition and preventive dental practice. There are several other ways in which fluoride can be used in the prevention of dental caries but each of the alternatives has substantial disadvantages compared with the fluoridation of water.

The justification for such a measure as the addition of fluoride to the water supplies of entire communities must rely on strong scientific evidence pointing not only to its effectiveness but to its safety, even though the recommended level in the public water supply is similar to that yielded by many natural sources. From the first, therefore, the safety of the fluoridation of water to the optimum concentration (1 milligram per litre) has been a paramount consideration, and fluoridation programmes were both preceded and accompanied by investigations of the health of populations exposed to fluoride in water. Allegations that fluoridation causes cancer have naturally given rise to great public concern. The present Report of the Working Party on the Fluoridation of Water and Cancer* draws together the many relevant epidemiological studies, including several analyses commissioned by the Working Party itself. The Report concludes that there is nothing in this extensive range of studies, covering altogether very large populations, to suggest that fluoride or fluoridation "is capable of inducing cancer or of increasing the mortality from cancer". Indeed the Report goes further and states that in view of the very large human populations which have been observed it can be concluded that "in this respect the fluoridation of drinking water is safe". The opposite opinion is still voiced in some quarters but the Report demonstrates that elementary misinterpretations of the facts are responsible for that conclusion.

The epidemiological studies reviewed by the Working Party provide the most direct evidence for the examination of the hypothesis that fluoridation causes cancer in man. Indeed, largely because of the extensive human data available on fluoride exposure, there has been relatively little work done on the effects of fluoride on cancer in animals. A more extensive body of research has been carried out using short-term animal tests, and tests with tissue culture systems, of a kind which can be relevant both to heritable abnormalities and to cancer.

Authoritative advice on all aspects of the evidence, in relation to the addition of fluoride to the drinking water of whole communities to achieve a concentration of 1 milligram per litre, has recently been obtained from the Department's independent expert scientific advisers. They considered all the available evidence on the biological effects of fluoride in short-term tests, and animal carcinogenicity tests, as well as the direct and extensive studies of human populations reviewed in the present Report. They concluded that there is no evidence leading to an expectation of hazard through the induction of heritable abnormalities, and no reliable evidence of any hazard to man in respect of cancer.

Throughout the world 260 million people (5 million within the UK) receive water to which fluoride has been added. Fluoridation is nearly forty years old and has been practised in the UK for nearly 30 years. The wealth of evidence which has been gathered and assessed during this period, including that presented in this report, justifies the conclusion that fluoridation is a safe and effective method of reducing dental decay.

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31.12.84

*under the chairmanship initially of Professor M Alderson, and subsequently of Professor E G Knox

CONTENTS

Preface
Summary

TABLES

FIGURES

SUMMARY AND CONCLUSIONS

1. INTRODUCTION
Origins of the Enquiry

S.1 The most recent general review in the United Kingdom of the evidence on the health effects of the fluoridation of water supplies was undertaken by the Committee of the Royal College of Physicians of London in 1976. The review concluded that fluoridation is safe, and in particular that "there is no evidence that fluoride increases the incidence of mortality in any organ".

S.2 Since the College Committee reported, the results of a number of new epidemiological investigations have become available, and the authors of some of the studies have claimed that increased cancer rates are associated with fluoridation. This Working Party was therefore set up to undertake a fresh review of the epidemiological studies.

Terms of Reference

S.3 The terms of reference of the Working Party were:

'to reappraise the published and otherwise available data and conclusions on cancer incidence and mortality amongst populations whose drinking water is either artificially fluoridated or contains high levels of fluoride from natural sources'.

2. A SHORT HISTORY OF THE FLUORIDATION AND CANCER ISSUE

S.4 Fluoridation of water supplies commenced in 1945 in the United States and Canada. Early trials in relation to the prevention of dental caries were accompanied by investigations of the rates of other diseases in fluoridated communities, and in populations in whose drinking water fluoride was present naturally. The results gave no reason to suspect any connection between fluoridation to the recommended concentration and any non-dental disease, including cancer.

S.5 In 1975, two investigators (Yiamouyiannis and Burk) concluded from an initial analysis that cancer mortality in the United States had increased as a result of fluoridation, a conclusion which they believed to be substantiated in their subsequent studies of cancer rates. Other investigators attributed this finding to technical deficiencies in the method of analysis and, on revising and extending the analyses, concluded that there was no evidence of an association between fluoridation and cancer.

S.6 In the United Kingdom, monitored local trials of fluoridation began in 1955 with no evident ill-effect, and subsequently several major areas were fluoridated. From 1979, Burk claimed that the fluoridation of Birmingham in 1964 had increased cancer mortality in that city. As in the United States, other authors pointed to technical deficiencies in these analyses and, on revising and extending them, found no association.

3. THE AMERICAN STUDIES OF YIAMOUYIANNIS AND BURK — (A) COMPARISONS OF CANCER RATES FOR A SINGLE PERIOD

S.7 The early studies by Yiamouyiannis and Burk compared cancer death rates, aggregated over a twenty-year period, in populations living in fluoridated and non-fluoridated areas. The authors claimed that the mortality from all cancers combined, and from certain cancers in particular, was greater in the fluoridated areas.

S.8 We have found that these analyses failed to consider the effects of other social and environmental differences between the groups in the comparisons, and failed to test whether or not the differences in cancer mortality between the groups were exceptional, given the variation within each group. In addition the data were sometimes inappropriately applied or unjustifiably

selected, and the analytical techniques displayed errors and questionable procedures.

S.9 We conclude that these studies did not provide a reliable indication of any association between fluoridation and cancer mortality. The investigations have been superseded by the subsequent studies of the trends in cancer death rates, by the same two authors and centred around the same communities.

4. THE AMERICAN STUDIES OF YIAMOUYIANNIS AND BURK — (B) STUDIES OF TRENDS IN CANCER RATES

S.10 Yiamouyiannis and Burk next explored the changes in cancer death rates over time, comparing ten fluoridated cities with ten non-fluoridated cities; four main types of analysis were presented.

S.11 First, crude cancer death rates were estimated for successive years for the two sets of cities. Both sets of cities initially showed a similar progressive increase, but the patterns began to diverge at about the time that fluoridation began, so that the set of fluoridated cities subsequently had a higher average crude cancer death rate than the set of non-fluoridated cities.

S.12 Conclusions based on the analysis of crude rates are notoriously unreliable, because the analysis ignores important characteristics of the populations under consideration, such as the proportions of old people, and of people of each sex and of different races. Each of these characteristics is known to influence cancer mortality, and the influence of age in particular is profound. The changes which occurred over time in these important characteristics of population structure were substantially different in the two sets of cities, and the initial analysis of crude cancer death rates took no account of these differences.

S.13 The second analysis presented by Yiamouyiannis and Burk was of cancer rates in four broad age-groups. The pattern of change shown in the earlier investigations was found to be limited to the two oldest age-groups, 45-64 years, and 65+ years. In the third analysis, these age-specific rates were combined by the method of direct standardisation.

S.14 These two additional analyses were also inadequate. The age-bands were too broad, and the interacting influences of age, sex and race on cancer mortality were not taken into account; further, the results for the 45-64 age-group were distorted by an important error in the data. Finally, the test of statistical significance used by the authors was inappropriate. A correctly used test has subsequently demonstrated that the reported differences between the average trends in cancer mortality for the two sets of cities were not exceptional — that is to say, they could easily have arisen as a consequence of the wide variation in the cancer rates for the individual cities, irrespective of fluoridation.

S.15 In the fourth series of analyses presented by Yiamouyiannis and Burk, age, sex and race were taken into account using an adaptation of the method of 'indirect standardisation'. The authors again concluded that cancer mortality was higher in the fluoridated cities, and that fluoridation was the cause. Their method of calculation, however, depended on unreliable estimates of population numbers, and their results differed from those of other investigators who based their analyses on accurate census data.

S.16 Yiamouyiannis and Burk failed to conduct a test of statistical significance. As with the earlier analysis of age-specific rates, a correctly used test has subsequently demonstrated that the slightly greater increase in cancer mortality (as calculated by their method) for the fluoridated cities was

not exceptional, and could easily have arisen as a consequence of the wide variation in the cancer rates for the individual cities, irrespective of fluoridation.

S.17 We conclude that each of these analyses by Yiamouyiannis and Burk were defective. None justifies their conclusion that fluoridation affects cancer mortality.

5. STUDIES OF THE "20 UNITED STATES CITIES" BY OTHER AUTHORS

S.18 The trends in cancer mortality, for the same cities and same period considered by Yiamouyiannis and Burk, were reanalysed in several studies. All of the authors took account of the influences of age, sex and race on cancer rates by using the routine method of indirect standardisation. These analyses were primarily based on population data for census years, and not on the less reliable estimates used by Yiamouyiannis and Burk for other years.

S.19 Yiamouyiannis raised a number of objections to the methods used in the initial reanalyses. He criticised the choce of the 'standard' population used in the standardisation procedure, the validity of the use of 1970 data for 'non-fluoridated' cities which had in fact been fluoridated for several months by that time, and the use of indirect rather than direct standardisation. Although it seemed unlikely that the results would be altered substantially, later investigators thoroughly explored the effects of modifications in these and other details of technique.

S.20 In none of these studies, including a series of reanalyses commissioned by us, were there any significant differences in mortality between the fluoridated and non-fluoridated cities, for cancers of all sites combined, other than those which were attributable entirely to demographic differences. Indeed, the only statistically significant difference found throughout all the studies of trends in these cities (including the studies by Yiamouyiannis and Burk) was the greater decrease in the standardised rate for genital cancers in the fluoridated cities, in the analysis, commissioned by us, of specific groups of cancers. Occasional results of this nature, unconfirmed in other studies, are to be expected when a large number of comparisons are made; such chance associations are not evidence of an effect of fluoridation.

6. OTHER STUDIES IN THE UNITED STATES.

S.21 The safety of fluoridation was investigated in many other populations in the United States. Cancer mortality and incidence were examined in populations in whose drinking water fluoride had always been naturally present, or had increased following fluoridation. None of these studies revealed an effect of fluoride or fluoridation on cancer rates.

S.22 An apparently positive association, between fluoridation and stomach cancer in males, arose in one study only. As with the finding, noted in paragraph S.20, of a negative association with genital cancers, this result has not been confirmed by the other studies, and therefore is not to be regarded as evidence of a real effect.

7. STUDIES IN THE UNITED KINDOM.

S.23 The early investigations in the United Kingdom concentrated on communities in whose drinking water fluoride occurred naturally. There were no associations with cancer, except for a possible excess of stomach cancer in part of one study. This finding was restricted to a group of three areas out of eighteen high-fluoride areas. The authors of the study concluded that fluoride was unlikely to be the cause.

S.24 No subsequent studies, including analyses commissioned by us, revealed any association in the United Kingdom between fluoride concentrations and cancer of any part of the body.

S.25 No association with cancer was found in any properly conducted studies of artificially fluoridated areas in the United Kingdom. Burk claimed otherwise, but we concur with other commentators in finding his methods of analysis to be wrong, and his conclusions false.

8. EPIDEMIOLOGY IN OTHER COUNTRIES.

S.26 Studies from ten other countries are available. The only conclusion of an association between fluoridation and cancer, from Canada, was based on an incorrect analysis of crude death rates. It was confirmed neither by the other Canadian studies, including an extensive investigation of communities fluoridated for up to 28 years, nor by appropriate analyses of cancer rates in Australia and New Zealand.

9. DISCUSSION AND CONCLUSIONS.

S.27 We have reviewed studies of cancer rates in relation to fluoride naturally present in drinking water and in relation to fluoridation of water supplies. We have found no evidence in these studies to suggest that fluoride or fluoridation is associated with increased cancer rates. Conclusions to the opposite effect, by others, arose either from failure to allow adequately for important demographic and socioeconomic differences between the compared populations, or from failure to take account of the range of cancer rates commonly observed irrespective of fluoridation. When cancer rates were analysed to take account of these matters, the patterns within fluoridated and non-fluoridated communities were found to be almost identical. Indeed, the populations with greater exposure to fluoride in water tended to have slightly lower rates of cancer mortality and incidence.

S.28 The available studies of artificially fluoridated communities cannot yet exclude a long-delayed effect — that is, an effect with a latency greater than twenty years from the initial exposure. However, studies of communities whose water supplies contain fluoride of natural origin would be expected to reveal long-term effects, and yet have not done so. This strongly suggests that artificial fluoridation will continue to be as safe in the very long-term as it has been shown to be in the four decades since its inception. It will of course be prudent to test the point directly, by continued surveillance of cancer rates in fluoridated areas.

S.29 Conclusions.

i) We have found nothing in any of the major classes of epidemiological evidence which could lead us to conclude that either fluoride occurring naturally in water, or fluoride added to water supplies, is capable of inducing cancer, or of increasing the mortality from cancer. This statement applies both to cancer as a whole, and to cancer at a large number of specific sites. In this we concur with the great majority of scientific investigators and commentators in this field. The only contrary conclusions are in our view attributable to errors in data, errors in analytical technique, and errors in scientific logic.

ii) The evidence permits us to comment positively on the safety of fluoridated water in this respect. The absence of demonstrable effects on cancer rates in the face of long-term exposures to naturally elevated levels of fluoride in water: the absence of any demonstrable effect on cancer rates following the artificial fluoridation of water supplies: the large human populations observed: the consistency of the findings from many different sources of data in many different countries: lead us to conclude that in this respect the fluoridation of drinking water is safe.

iii) The routine monitoring of public health has been an important feature of many fluoridation programmes, and has contributed to the confidence with which we can assert the safety of fluoridation with respect to cancer. We recommend that such monitoring should continue.

CHAPTER 1

INTRODUCTION

ORIGINS OF THE ENQUIRY

1.1 The first experimental fluoridation* of drinking water for the prevention of dental caries was conducted in the American town of Grand Rapids in 1945. This experiment was followed by a number of other comparative trials in the United States, Canada, the United Kingdom and other countries. These trials confirmed that the addition of certain compounds of fluorine to water, so as to increase the level of fluoride to one part per million, reproduced the relatively low rates of dental decay reported from places where fluoride, at about that level, was naturally present in the water. There were no evident ill-effects from fluoridation, and it was subsequently extended to many other communities; some 260 million people now receive artificially fluoridated drinking water.

1.2 Some opposition to fluoridation seems to have occurred from the first, on grounds both of personal rights and of fears about safety. As a result, decisions to fluoridate were often taken only after extensive scientific re-examinations of the evidence, or even judicial enquiries. In spite of reassurances as to the safety of fluoridation from the original trials, from studies of the health of communities with naturally-occurring fluoride in their water supplies, and from these occasional reanalyses and enquiries, there were continued claims of a variety of ill-effects. The claims were often pressed through political or legal channels or in the lay press, rather than in the scientific literature. After expert scientific scrutiny, in a series of national and international enquiries, none of the claims were considered to have been substantiated.

1.3 One of the allegations has been pressed with particular vigour. It is that fluoridation causes cancer. Despite a number of published scientific re-examinations and refutations, the claim has been repeatedly asserted. The public and their representatives have gained the impression that there is at the least a scientific controversy, and programmes for the wider introduction of fluoridation have undoubtedly been hindered.

1.4 This is too important an issue not to settle to the satisfaction of the public at large as well as of the scientific world. If the claim were correct, it could be argued not only that fluoridation should cease but also that naturally occurring fluoride should be removed from water, that fluoride should no longer be added to toothpaste, and that intake of fluoride from tea and other high-fluoride foodstuffs should somehow be reduced. If the claim were demonstrably false, there would be no impediment, at least on this ground, to the programme of fluoridation. If there were residual doubts, however small, then the balance of risks and benefits would have to be reassessed.

1.5 The most recent review in the United Kingdom of fluoridation in relation to health was undertaken by the Royal College of Physicians in 1976. New evidence and new analyses have appeared since that time. This Working Party was formed in 1980 to review the whole of the existing epidemiological evidence relating to fluoridation and human cancer.

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*Technical terms are defined in the Glossary.

TERMS OF REFERENCE

1.6 Our terms of reference were "to reappraise the published and otherwise available data and conclusions on cancer incidence and mortality amongst populations whose drinking water is either artificially fluoridated or contains high levels of fluoride from natural sources".

1.7 We were asked to give particular attention to the more recent material offered in support of statements that fluoridation or fluoride has caused cancer, especially where this material had not been published in widely circulated scientific journals or had not been fully considered in earlier reviews. We have been asked to explain the points at issue in language accessible to non-scientists without specialized knowledge of the subject matter or the technicalities of analysis, in order to permit those with particular responsibilities for fluoridation policy, and the general public, to resolve any conflicts or uncertainties and to make their own judgements.

1.8 We have tried to trace and consider every study and report on the subject, whether published in scientific journals or appearing in the course of law reports, proceedings of official committees, and so forth. We obtained additional information from the authors of some of the studies, to assist with our assessments, and we are grateful for the help given. Further, we commissioned from amongst our members a series of checks, and even full reanalyses, of some of the most important data and results. A number of the papers referred to this report are the subsequently published fruits of those commissions.

1.9 It was not part of our brief to review the dental or other possible benefits of water fluoridation, nor to consider alternative forms of fluoride supplementation. We have not discussed claims of harm other than the alleged cancer risk. Questions of freedom of choice, and of the law and its interpretation, are for others.

NATURE OF THE EVIDENCE TO BE CONSIDERED

1.10 Three main areas of scientific evidence bear on the question of fluoridation and human cancer. The first consists of direct measurements and comparisons of the incidence of cancer and the mortality from cancer in human populations exposed to different levels of fluoride in drinking water; our central task was the assessment of this epidemiological evidence. The second area consists of evidence from laboratory experiments in which the effects of exposing animals or plants or isolated tissues or cells to fluoride are observed; although we refer to some early studies of this nature in our historical chapter (Chapter 2), we have not reviewed this evidence, which is under consideration by other advisory bodies. The third area consists of the extensive body of existing knowledge concerning the ways in which cancers originate and develop, and concerning the parts which chemicals and other agents can play in that process; as an understanding of some aspects of established knowledge in this area is important for the proper interpretation of the epidemiological knowledge, we summarise the relevant aspects in Chapter 9 (para 9.4 onwards).

1.11 The epidemiological evidence is direct, and the argument from it is in principle simple. However, the numerical foundations on which it is based are sometimes complex, and the analytical methods may be intricate. Our report reviews some 70 studies using data from twelve different countries, although many were small investigations, or consisted of reanalyses of earlier published data. In practice, the most important issues are effectively covered by a handful of these enquiries. We shall refer to all the investigations known to us, but our report will deal in special detail with this relatively small but important group.

1.12 The apparent complexity surrounding the interpretation of the epidemiological evidence on fluoridation and cancer, in particular that relating to the United States and the United Kingdom, has sprung not so much from the data themselves as from questions concerning the propriety of the methods chosen for analysis, comparison and presentation. Such questions of technique are therefore central issues in our review, and some of the questions raised about the methods used in the various studies are of great importance. Most of the variations in technique, however, turn out to have no important effect on the conclusions to be drawn from the data. The arguments which have surrounded such minor points have sometimes diverted attention from the major issues which we will highlight in this report.

1.13 Almost all of the studies which we have seen have been based on the statistics of exposure to fluoride in drinking water and the statistics of cancer incidence and mortality, in whole communities. In many cases the data have been collected as part of a routine public health monitoring service. We have encountered only one study which could be interpreted in terms of measured fluoride intakes in individuals (Stocks, 1958). This depended on estimating different consumptions of tea, infusions of which contain fluoride in concentrations up to 4.7 ppm (Walters et al., 1983).

1.14 Within this almost universal framework of studies on whole communities rather than indviduals, the available studies differed in the following ways:
   a) by using either mortality data (i.e. data on the deaths from cancer) or incidence data (i.e. data on the number of newly diagnosed cases);
   b) by using data on cancer in different parts (sites) of the body or data for all types of cancer combined;
   c) by comparing artificially fluoridated with non-fluoridated areas or comparing areas with different natural levels of fluoride;
   d) by using simple comparisons of rates (i.e. comparing cancer rates for a single period) or comparisons of time-trends (i.e. comparing changes in cancer rates between the beginning and end of a period).

1.15 More important than the above differences was the degree to which allowance has been made, in the analyses and interpretations, for differences in the demographic and socioeconomic structures of the compared populations, and for different patterns of change in these respects.

THE SCIENTIFIC APPROACH

1.16 We were asked to examine a question of cause and effect, and to do so on the basis of direct observations upon human populations; that is, through epidemiological studies. In assessing those studies, however, it is important to realise that epidemiological research is a minefield for the unwary or inexperienced. Errors may arise at all stages, from the planning of a study to the expression of its overall conclusions. The common errors are well documented and texts of epidemiological and statistical methods describe procedures for avoiding them. The avoidance of error constitutes a major preoccupation of the authors of many of the reports we have read and therefore of our own review. As we shall see, the identification of errors supplies the key to the understanding of the issues in hand.

1.17 Epidemiological research can be thought of as involving three main stages. The first consists of the collection, classification and presentation of the data.

15

1.18 The second stage consists of a series of statistical analyses designed to eliminate certain well recognised sources of error and to present all the valid results which can be drawn from the data of an individual study in convenient, summary form. Usually, the analyses will consider in turn:

a) whether any form of association exists between the factors under study: in this instance, for example, whether certain cancer death rates are higher in a 'high-fluoride' area than in a 'low-fluoride' area;

b) if so, whether some other difference between the areas may account for the difference in cancer rates. In particular, there may be a greater proportion of old people in the 'high-fluoride' area; there may be disparities in social or economic factors themselves known to be associated with different risks of cancer;

c) whether the remaining differences in cancer rates between the areas could merely be a consequence of random fluctuations in those rates; that is, could be due to 'chance'.

1.19 These first two stages are relatively formal, so that it is usually possible to say whether the methods used in a given study were correct or incorrect.

1.20 The third stage in epidemiological research is the interpretation of the results, leading to a conclusion on whether a cause and effect relationship has been demonstrated or not. Even where evidence of an association survives the analyses indicated above, it must be interpreted in the light of its consistency with findings of studies done elsewhere, and in the context of other biological knowledge; it is always unsafe to base firm conclusions on the results of a single study. The evidence should be considered as a whole, before attempting to reach a conclusion as to whether there have been positive results from the work in hand, or not. This third stage is less formal than the preceding stages, and calls particularly for experience and trained judgement. At each stage, however, errors of procedure or logic can occur.

1.21 In the following three sections (paras 1.22 to 1.49) we enlarge upon some of the problems which arise at each of the three stages of epidemiological research, and we consider some of the implications for us in our task of deciding whether a cause and effect relationship may exist between fluoridation and cancer. Readers who are familiar with the principles involved may prefer to move immediately to paragraphs 1.50 onwards, where the structure of the report is outlined.

ERRORS IN DATA

1.22 Like all scientific data, routinely collected health statistics are subject to error. Causes of death or sickness may be incorrectly diagnosed, or misclassified. Mistakes of identification and errors in the coding of personal and social characteristics may occur. For different reasons both mortality data and incidence data tend to under-represent the true number of cases of cancer; in the first instance, some patients are cured or die from other causes, while, in the second, registration of newly-diagnosed cases of cancer is not a legal requirement and is carried out with variable thoroughness.

1.23 The estimates of fluoride levels in water may also be inaccurate, or assigned to inappropriate populations. The boundaries for water supplies may not correspond to the boundaries relating to census returns and, indeed, the boundaries may change during the period under study.

1.24 Where official population statistics are available for census years only, it will only be possible to use mortality figures for intervening years by

making assumptions about the intercensal population numbers. The resulting population estimates, and hence the death rates, will tend to be less reliable when they refer to years distant from a census year.

1.25 Errors of arithmetic and transcription may occur in any of the types of data. In spite of the checks normally employed by statistical agencies, mistakes are sometimes found.

1.26 We encountered examples of all these types of error in the course of our examinations. The acceptability, or otherwise, of the data is not necessarily a simple matter, but requires some judgement of the reliability of the procedures used for obtaining and summarising the raw numbers.

ERRORS OF ANALYSIS

1.27 It is at this stage that the opportunity for arithmetical error is greatest. Not only may numerical mistakes be made, but also the choice of the arithmetical method for handling the data may be illogical. For example, a death rate per thousand white males in a community, multiplied by the number of all the people in that community (females and non-whites included), will result in a meaningless number. Such errors have been a source of false conclusions in some of the studies we have considered.

1.28 The most fundamental errors which may occur are to ignore the role which (a) confounding factors or (b) chance may play in creating apparent differences between one investigated population and another, or to fail to use sound methods when taking account of them in analyses. Each of these topics is considered separately below and the precautions necessary for avoiding errors are described.

Confounding factors

1.29 Groups exposed or not exposed to fluoride, and whose cancer rates are to be compared, will almost certainly differ in respects other than fluoride exposure itself. Some of these other differences will be related to the risk of developing cancer. One group may include more elderly people; the groups may be socially different, may live in different environments and may pursue different lifestyles.

1.30 The risk of developing various cancers is known to differ in each of these circumstances. If certain demographic or socioeconomic factors should happen to be associated (for whatever reason) with fluoridation, or with different natural levels of fluoride in water, then a misleading association between fluoride and cancer may result. Such factors are then known as 'confounding factors'.

1.31 There are two ways of avoiding the spurious associations for which confounding factors are responsible. The first method is used in the initial design of a study, when an attempt is made to select groups which are identical except for the exposure to be examined. It is rare for this to be completely feasible in the study of human populations, and it is almost always necessary to have recourse to the second method. This involves the use of additional statistical procedures by which, as far as is possible, the crude data are adjusted to take account of the demographic differences between the exposed and unexposed groups. It is sometimes possible to incorporate adjustments for selected socioeconomic differences.

1.32 It is clear, from what has already been said, that 'crude' cancer rates (that is, rates uncorrected even for basic demographic characteristics such as the age-structures of the populations) do not provide an adequate basis for

comparisons between whole populations. One remedy is to subdivide the data so that it is possible to compare the rates specific to a particular sector of the population (for example, males aged 25-29 years inclusive); another remedy is to correct the rates, at least for age differences and preferably also for sex differences, using one or other of the available 'standardisation' procedures which are described in Appendix 1. Failure to proceed to such analyses, or improper application of the methods, is a potent source of error.

1.33 The 'confounding factors' are not all of equal importance. The most likely explanation of a difference in crude cancer rates between two populations is a difference in the demographic structures of the populations, in particular the age-structure. Differences in the proportions in the populations of either sex may also be important, especially if the rates of specific cancers are being studied. Nevertheless, standardisation for age and sex is not always sufficient. American data are often corrected for the proportion of whites and non-whites in the population. Not only the different racial groups, but also the various socioeconomic and occupational groups, may show different patterns of disease. An explanation is sometimes to be found in differences of behaviour (smoking habits, for example), or in occupational exposure to substances which are known to increase the risk of developing cancer, but the precise reasons for differences in the patterns of disease are often unknown. Rates standardised for age and sex may be corrected for confounding social and economic factors by further standardisation procedures, but the data needed for correction are often not available. One practical implication is that the compared groups should preferably be as similar as possible in socioeconomic terms, and not too distant geographically.

1.34 However carefully the appropriate procedures are followed, it is never possible to be sure that all other factors have been sufficiently taken into account in the design and analysis of a study. A statistically significant association found after standardisation for demographic and other known relevant factors may yet be due to an unidentified 'confounding factor'. It is always necessary to examine a number of independent studies, to compare them with one another, and to look at their results in the light of other knowledge, before arriving at a conclusion.

Chance

1.35 Even where different communities have been chosen to be as similar as possible in all relevant respects, and when their exposure to factors known to be associated with cancer risk are apparently very similar, there will nevertheless, in practice, be small residual differences in the cancer rates measured, especially over limited periods. Populations show an apparently intrinsic and unavoidable degree of variation in their response to agents of disease, a variation customarily designated as being 'due to chance'. Therefore, there is a 'random' element in the differences in rates of disease found in different populations. If communities consist of small numbers of people, the random element is relatively large. Fortunately, the amount of variation which is likely to occur from such random processes can be calculated.

1.36 Thus, an observed difference between the corrected cancer rates of two sets of communities can be tested to see whether it is greater than would have been likely to occur by chance alone. When it is sufficiently unlikely that chance could account for such a difference, it is said to be 'statistically significant'. (A fuller explanation of statistical significance is given in Appendix 2).

1.37 Care is needed in interpreting the results of tests of 'statistical significance', for they are often misunderstood. First, such tests provide only a statement of probabilities, and never absolute proof. Second, a 'statistically significant' result is not necessarily 'significant' in the sense of being biologically important, and it is essential not to confuse the two different meanings which can be attached to the word. Third, these tests give no direct indication as to the reason for a difference. A demonstration of statistical significance is but one step in an argument.

1.38 A particular problem may arise in a large investigation, where is is possible to compare exposed and non-exposed groups in many different ways. The groups can be subdivided by age, sex or by other characteristics, and the cancers themselves can be subdivided according to their individual sites, and then regrouped in many alternative ways. This permits very detailed analysis, and helps to prevent a true cancer-producing effect from being obscured. However, because of the large number of comparisons it is likely that there will be results which would be rated as 'statistically significant', but which would not indicate a real effect. For example, a single result with a chance of random occurence of not more than 1 in 20 is often held to be 'statistically significant'; in 60 comparisons one would therefore expect to find three results which are 'statistically significant' but have occurred by chance alone. This confirms the principle that it is always unsafe to base a conclusion on isolated 'significant' results, while ignoring the rest of the evidence.

1.39 The method chosen for the calculation of statistical significance should depend on the nature of the study which is being performed. Failure to assess statistical significance is reprehensible, but use of an incorrect test can be misleading. We have encountered both defects among the studies which we have reviewed.

ERRORS OF INTERPRETATION
Attributing Causality

1.40 We have seen that a question of cause and effect arises only when associations have been demonstrated not to be due to confounding factors, using suitable analyses of reliable data along the lines already indicated, and when the degree of their statistical significance has been determined. The subsequent process of interpretation of the evidence, in order to decide whether the relationship is one of cause and effect, is less formal than the processes of collecting and analysing data, but certain criteria can guide the investigator. Bradford Hill (1977) provides a helpful list of points to consider when assessing whether an association is causal or not. He sets as the fundamental question 'Is there any other answer which is more likely than cause and effect?''. However, 'likelihood' is here a matter for experienced scientific judgement, formulated in the light of all the evidence, rather than something which can be measured or formally demonstrated. Bradford Hill emphasizes that none of his criteria ''can bring indisputable evidence for or against a cause-and-effect hypothesis and equally none can be regarded as a sine qua non).''

1.41 The criteria include the strength of the association, its consistency in a sufficient number of different circumstances, and the presence or absence of a graded relationship (for example, a progressive increase or decrease in cancer rates over a range of fluoride levels). In the present context, additional criteria would be site-specificity (is there evidence of an association with cancer rates for specific organs, for example those which are particularly exposed to fluoride?), and the existence or otherwise of a plausible biological mechanism by which fluoride could cause cancer.

Formulating and Testing Hypotheses

1.42 Scientific knowledge of any subject is advanced by alternating steps in which, in simplified terms, a hypothesis (that is a tentative theory) is first formulated and then thoroughly tested by research. If this process is to be fruitful and error is to be avoided, each hypothesis must be closely defined and the logic by which the results of research are used to test it must be impeccable. (The actual processes of individual scientific investigations are, of course, more complex than that and the detailed steps are rarely made explicit). It is essential there should be no major flaws in the underlying reasoning. During our enquiry we have detected some crucial errors of logic in the formulation and testing of hypotheses. Some of the most pertinent points which need attention if false conclusions are to be avoided are outlined in this section.

1.43 Before a hypothesis is accepted, it must pass three tests. It must be shown to be valid, that is to say that the facts from adequate research must not contravene it. It should also be comprehensive and unique. It can be regarded as comprehensive only when it explains all the material facts; it is unique only when the facts on which it is based cannot be explained in any other way. A common error is to accept a hypothesis on the basis of isolated supportive findings without looking at the evidence as a whole.

1.44 A hypothesis may be suggested by reasoning from established knowledge or by analysis of a set of data. In the latter case it is mandatory that it should then be tested by analysis of an independent set of data. If the cancer rates used in one study include a substantial number of the cancer cases used in another study, then the two studies are not separate tests of the hypothesis.

1.45 Cancer is not one disease, but a collection of diseases. An initial hypothesis that fluoridation, for example, causes an increase in the rate for all cancers combined should be further refined. Is it suggested that there is an increase of every type of cancer, or only an increase of cancers of certain sites? It may be that a group of studies appears to support the initial hypothesis, but failure to examine the rates for specific cancers, or inconsistency between studies in the types of cancer which appear to show a response, means that the studies do not support either of the more sharply defined hypotheses.

1.46 Hypotheses are tested ultimately through reference to observations. Compatability with existing scientific knowledge (that is with other well-supported hypotheses) is also important but it is not logical to validate one hypothesis by an argument based on acceptance of another unsupported hypothesis.

1.47 The only powerful test of a hypothesis is the failure of powerful attempts to disprove it. There is no other method of 'proof'. To search specifically for evidence to buttress a favoured hypothesis can be a most potent source of error.

Burden of Proof

1.48 Scientists will not normally accept a hypothesis unless it is supported by a sufficient range of sound evidence, is concordant with other biological knowledge, and seems the most likely of the alternative explanations. Relationships of cause and effect are normally denied until they have been positively demonstrated. The burden of proof lies with the proponent of the hypothesis. However, those concerned with the implementation of public health procedures, and faced with the possibility that their actions could cause harm, naturally try to seek the best assurances of safety. This raises a difficult

scientific problem, because it is axiomatic that the <u>absence</u> of harmful effects from any action whatsoever can never be strictly proved, and certainly not in advance of the action.

1.49 If there is to be any advance at all in public health, the only sensible approach is to identify all <u>reasonable</u> hypotheses of potential harm, and then to test them on a sufficient scale and in several different ways. If no consistent evidence in support of these hypotheses is found in investigations which have been correctly performed, then we can feel entitled to regard the absence of demonstrable harm as a reassurance of safety.

THE STRUCTURE OF THE REPORT

1.50 We shall draw our conclusions together in the final chapter of our report, in the light of the considerations outlined above. The detail of the epidemiological evidence is presented in Chapters 3 to 8, preceeded by a historical outline in Chapter 2.

1.51 Chapter 2 describes the origins of fluoridation as a public health measure, and then traces the manner in which the possibilities of harmful effects were first raised and then pressed; in particular, how the hypothesis that fluoridation might cause cancer arose and persisted. The subsequent pattern of response and counter-response is then described. This brief historical perspective is intended to give the reader an appreciation of the pathways through which these questions have been pursued; it is hoped that it will provide a context in which the pattern of the evidence as a whole will be more readily grasped.

1.52 The cancer hypothesis has been advanced principally by Yiamouyiannis and Burk following their examinations of data from the United States. For this reason, Chapters 3 to 6 discuss the various studies of material from the United States. Chapter 3 considers the earliest group of studies by Yiamouyiannis and Burk, based on comparisons of the cancer rates in 'fluoridated' and 'non-fluoridated' populations for one particular period. Subsequently they compared changes in cancer rates; these 'time-trend' studies, which now form the principal basis for their hypothesis, are considered in Chapter 4.

1.53 In Chapter 5 we discuss the papers of those authors who responded to the 'time-trend' studies in Chapter 4 by reassessing the same data, but using different statistical methods. Much of the apparent complexity of the issue has arisen as a result of the different interpretations of the data by these authors on one hand, and by Yiamouyiannis and Burk on the other.

1.54 Investigations into the question of an association between fluoride and cancer had been conducted long before the studies by Yiamouyiannis and Burk. In the United States, as elsewhere, the rates of various diseases, including cancer, were initially compared in populations whose drinking water contained different natural levels of fluoride; when fluoridation schemes commenced, disease rates were monitored in the fluoridated communities. The results are described in Chapter 6, in which we also comment upon those later investigations in the United States which considered populations other than those chosen by Yiamouyiannis and Burk.

1.55 In the United Kingdom, there was a similar sequence of investigations of cancer rates in areas with different natural levels of fluoride, and of monitoring studies in artificially fluoridated areas. Particular attention was drawn by Burk to apparent evidence of a harmful effect of fluoridation in

Birmingham; other authors published reanalyses and supplementary studies which did not confirm Burk's conclusions. The studies in the United Kingdom are discussed in Chapter 7.

1.56 The remaining investigations, from countries other than the United States and the United Kingdom, are presented in Chapter 8.

1.57 Chapter 9 discusses and reappraises the epidemiological evidence as a whole, and presents our conclusions.

1.58 The principal technical terms are defined in the Glossary. Appendices 1 and 2 give fuller explanations of Standardisation and of Statistical Significance. Appendix 3 sets out the results of our investigation of cancer incidence rates in relation to concentrations of fluoride naturally present in water in the United Kingdom.

CHAPTER 2

A SHORT HISTORY OF THE FLUORIDATION AND CANCER ISSUE

THE BACKGROUND: THE ORIGINS AND INTRODUCTION OF FLUORIDATION

2.1 The experimental introduction of fluoridation in the United States in 1945 had its roots in observations of the effects of high levels of fluoride naturally present in some water supplies. The high incidence of dental mottling in certain populations was recognised from the end of the 19th century. In a description of the Chiaia area of Naples, published in 1892, Benedetto Croce noted that the drinking water was responsible for badly stained teeth (Croce, 1892, quoted in McClure, 1970).* Subsequent investigations, principally in the United States, continued to implicate the water supply (e.g. Black and McKay, 1916, and other papers by these authors) but it was not until 1931 (Smith et al., 1931) that very high natural levels of flouride were shown to be responsible. Meanwhile, an association between dental mottling and a low rate of dental caries had been noted (Bunting et al., 1928). Extensive surveys in the 1930s and early 1940s (e.g. Dean, 1938, and other papers by this author) confirmed the association and demonstrated that flouride was the common factor, so confirming speculation dating back to 1874 (Erhardt, 1874) that flouride might act against tooth decay. It was shown later that water containing fluoride at a level of 1 ppm (1mg per litre) did not produce noticeable dental mottling, but that it was still associated with relative freedom from caries when compared with water containing 0.2 ppm or less (Dean et al., 1942 and related studies). By the late 1930s the possibility of the deliberate addition of fluoride to water to reproduce this benefit was under discussion in the USA, although at first the proposals were opposed by the American Dental Association and the US Public Health Service.

2.2 Fluoride in large amounts is severely toxic, causing a variety of actute ill-effects and, in extreme cases, death. The safety of artificial fluoridation was therefore a key question from the start. Guidance was available from places where people had been exceptionally exposed to fluoride. Skeletal fluorosis, a disease of bone which can be crippling in severe cases, occurred in parts of the world with extremely high natural cocentrations of fluoride in water (e.g. Shortt *et al.*, 1937). This disease had also occurred following exceptional industrial exposure (Roholm, 1937). No other non-dental disease was reported to result from these high exposures, nor was any non-dental disease reported from the use of the moderately high-fluoride waters which were associated with dental mottling. In the period before the introduction of fluoridation, therefore, most research was directed at the way in which the healthy body deals with fluoride and on effects on teeth and bone, although two studies, one in the United States (Leone *et al.*, 1955) and one in the United Kingdom (Weaver, 1944), dealt with a wider range of health questions, in relation to fluoride in water. It is clear, however, that much weight was placed on the fact that numerous population groups have "drunk naturally fluoridated water containing 1 ppm or more during their lifetimes" and that "medical practitioners and specialists in these areas have never detected and defined a systematic aberration in health of any kind related to the fluoride consumed (except mottled enamel in endemic areas)". (WHO, 1958).

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*McClure (1970) gives a full and interesting account of the early history of fluoridation.

2.3 From 1945 small comparative trials of fluoridation were started in the United States and Canada, in order to confirm the expected reduction in tooth decay and to test the technical procedures for fluoridation. Some drinking waters with low fluoride levels were supplemented to a level of about 1 ppm, and the fluoridated districts were compared with similar, but untreated, low-fluoride districts and sometimes also with districts with water containing natural levels of fluoride close to 1 ppm. Health studies, discussed later, were included in two of the trials. In some others doctors were asked to report any ill health which they thought might have arisen from fluoridation. By August 1950 the emerging results had confirmed the expected reduction in dental decay and the United States Public Health Service recommended the wider introduction of fluoridation. Monitoring continued in trial areas and mortality statistics from communities served by waters with naturally high concentrations of fluoride were analysed.

2.4 A number of major American cities commenced fluoridation of their water supplies in the period from 1952 to 1956 but the measure was encountering increasing opposition. This opposition was partly based on the contention that fluoridation infringed individual freedom but in part it was a response to claims that fluoridation had many kinds of adverse effects on health. These claims were generally pressed through political or legal channels or in the lay press and without evidence being submitted in advance to the usual processes of scientific review. Expert committees in several countries have since reviewed the evidence on which the claims were based, and all have concluded that the claims were ill-founded. Proposals to introduce fluoridation in the United States were increasingly referred to public referenda as well as to public enquiries and courts of law. Some of the referenda went against fluoridation but the measure was nevertheless slowly extended until, by 1980, some 46 per cent of the total population of the United States was supplied with artificially fluoridated water (Department of Health and Human Services, 1984).

2.5 In the United Kingdom comparative trials were started in 1955 and 1956, initially comparing four fluoridated areas (Andover, the Gwalchmai zone of Anglesey, Kilmarnock and Watford) with four non-fluoridated areas (Winchester, the Bodafon zone of Anglesey, Ayr and Sutton). As a result of local opposition, Andover discontinued after two years and Kilmarnock after six; on the other hand, in 1964 the County Council decided that children in the Bodafon zone of Anglesey, which had been one of the non-fluoridated areas included in the study, should receive the benefits of fluoridation (DHSS *et al.*, 1969). These trials had been recommended in the report of an official mission (Forrest *et al.*, 1953) which had been sent in 1953 to study the American experience of fluoridation. As in the United States, the trials were designed primarily to assess dental benefit, and the technical procedures of fluoridation. By then the reassuring results of the American health studies were available and a conference of experts convened by the Medical Research Council recommended that British research concerning health and fluoridation in the selected areas should be directed towards reasonable hypotheses only, but that the relevant vital statistics be monitored and specific investigations instituted where indicated (Ministry of Health *et al.*, 1962). Twelve specific non-dental investigations* were carried out, none of direct relevance to this report; in addition, mortality rates for naturally high and

*The subjects were: osteochondritis juvenalis of spine; fluorine content of bone; malnutrition and susceptibility to dental fluorosis; incidence of mongolism; peptic ulceration; school absenteeism; anaemia of pregnancy; thyroid size; rheumatic diseases; fluorosis in farm animals; fluoride from boiled bones; intake of airborne fluoride. The last three were investigated in relation to implications for dietary intake of fluoride.

low-fluoride areas were compared (Heasman and Martin, 1962) and every medical practitioner in the trial areas was asked at intervals for information as to any harm arising out of fluoridation; two patients only were reported, and their symptoms were found not to be attributable to fluoridation (Ministry of Health *et al.*, 1962; DHSS *et al.*, 1969). The results of the trials and of the various health studies were judged satisfactory and the Government announced its support for fluoridation in December 1962; fluoridation has since been extended to some 10% of the population, notably to the Birmingham area in 1964.

EARLY STUDIES OF FLUORIDATION AND CANCER: 1944-1975

2.6 Cancer was included in several of the early studies of fluoride and health already referred to, but usually without emphasis and simply as one of the major disease categories which might feature in any broadly based study. Studies which dealt specifically with cancer were few in number.

1944: United Kingdom

2.7 The first published reference to cancer and fluoride is from this country where Weaver (1944) included cancer in his analysis of mortality for South Shields, a town with a high level of fluoride naturally present in its water supply (see Chapter 7).

1945-1954: United States

2.8 Cancer seems to have been included early amongst the claims of ill-effects which followed on the official endorsement of fluoridation in the United States. The origin of the suggestion is not clear but most attention seems to have been given to a series of reports on experiments in mice, carried out in Texas from the late 1940s. (A Taylor, 1954; Taylor and Taylor, 1965); the results of these experiments in animals have not been accepted by subsequent authoritative reviews (e.g. IARC, 1982). Two references to claims of increased or excess cancer in human populations date from the early days of fluoridation in the United States. Perkins (1952, quoted by Swanberg, 1953) reported on trends in the numbers of deaths in Grand Rapids, the site of the first experimental American fluoridation scheme. Following the introduction of fluoridation in San Francisco in 1952, reports circulated widely that the incidence of cancer of the thyroid had increased substantially there; these reports were not based on official statistics and Fletcher (1962) traced their origin to incorrect statements concerning both the timing of fluoridation and the thyroid cancer trends. Two papers were published in brief but immediate refutation of the early claims. E Taylor (1951) responding to pre-publication reports of the experiments in mice by A Taylor, and Swanberg (1953) repsonding to Perkins, both included some analyses specifically on cancer mortality statistics in their replies.

2.9 The other American fluoride studies from this period dealing with cancer included it simply as one of a number of important disease categories. Although these studies were all published soon after the reports of Perkins and A Taylor were made public, some of them had been started earlier and they do not seem to have been planned as a response to those reports. The studies fell into three groups. The first group consisted of two studies of individuals in small communities which were supplied with water containing exceptionally high natural levels of fluoride (Leone *et al.*, 1955; Geever *et al.*, 1958). The second group used the mortality statistics for much larger communities with moderately high levels of fluoride naturally present in the water supply, comparing these with nearby communities supplied with low-fluoride water. A study based on 1940 statistics from Illinois (1952) was followed by a national study using statistics for 1949 and 1950 (Knutson 1954; Hagen *et al.*, 1954). All these studies of communities with fluoride naturally present in the water had the advantage that much of the population

had been exposed to fluoride in drinking water throughout life. The third group analysed trends in mortality, using data from two of the early fluoridation trials, and comparing the trial community with a non-fluoridated community. The trials were those in grand Rapids (Knutson, 1954) and Newburgh (Schlesinger *et al.*, 1956). None of the reports indicated a risk of cancer from fluoride or fluoridation. (Details of all the early American studies are in Chapter 6).

2.10 In the past 20 year period up to 1975 no further studies of cancer in populations in relation to fluoride in water seem to have been undertaken in the United States. Experiments in animals and plants continued, however, and reports began to appear, largely from one author (e.g. Mohamed *et al.*, 1966), of mutagenic effects from fluoride. No published expert scientific review has accepted these reports. Assertions that fluoridation causes cancer, amongst other ills, continued to feature in the many legal or legislative hearings and referendum or ballot campaigns that have characterised the fluoridation controversy in the United States. Meanwhile, epidemiological research continued elsewhere.

1954-1975: United Kingdom

2.11 The mortality statistics for areas in the United Kingdom with water supplies naturally high and low in fluoride were compared in 1954, before the British fluoridation trials began. It was reported that no difference had been found which could be interpreted as indicating any harmful effect on health (Ministry of Health *et al.*, 1962); the details of this first analysis were not published. The surveillance of the statistics continued and, in 1962, Heasman and Martin reported that there were some differences between the high — and low-fluoride areas including a relative excess of stomach cancer in certain of the high-fluoride areas. The results in different parts of the country were inconsistent, and Heasman and Martin considered it very unlikely that this, or any of the other differences noted, was caused by fluoride.

2.12 Schatz and Schatz (1972), in a paper primarily concerned with other matters, stated in passing that there had been an increase in the number of cancer deaths in Birmingham (UK) immediately following fluoridation; there were no supporting data or analyses.

2.13 In 1973 the Royal College of Physicians of London set up a committee to advise on medical aspects of fluoridation, in response to a request from the dental profession. Cancer was one amongst many topics dealth with. The report (Royal College of Physicians, 1976) was able to take account of two further papers on British cancer statistics (Kinlen, 1974; Nixon and Carpenter, 1974) which reported no significant differences in cancer rates between high- and low-fluoride areas, or between fluoridated and non-fluoridated neighbouring areas. The report was also able to take account of initial reports of events in the United States in 1975 described below. It concluded that there was "no evidence that fluoride increases the incidence or mortality of cancer in any organ". (The evidence from the United Kingdom is reviewed in Chapter 7).

1954-1975: Other Countries

2.14 Studies, of limited scope, of the relationship between fluoride naturally present in drinking water and indices of various diseases, including cancer, were published during this period from the Soviet Union (Knizhnikov, 1959), Italy (Mirisola and Cruciani, 1964), and Sweden (Biörck *et al.*, 1965). None reported a cancer risk from fluoride. (These studies are reviewed in Chapter 8).

LATER STUDIES IN THE UNITED STATES: 1975-1978

2.15 The question of cancer and fluoridation came into sudden prominence in 1975 with a series of public statements by Yiamouyiannis and Burk. The evidence in these statements, and all that followed, is discussed in detail in the subsequent chapters of the report; our purpose here is simply to clarify the complex pattern of events and to indicate the context of the various statistical analyses which we are to discuss. The public controversy concerning cancer and fluoridation appears to have started in earnest in January of 1975, a few months before a referendum on the introduction of fluoridation in Los Angeles, California, with the issue by the National Health Federation of two publicity handouts (Yiamouyiannis, 1975a, 1975b) announcing that cancer death rates had been shown to be higher in fluoridated than non-fluoridated American cities. The National Health Federation, a private organisation based in California, had earlier announced its opposition to fluoridation. Yiamouyiannis had been appointed as Science Director of the Federation in June 1974 and it was he who had done the study referred to above. His later co-author, Burk, had retired from a senior position with the United States National Cancer Institute the previous year.

2.16 In 1974 the National Cancer Institute (NCI) had published for the first time the statistics of cancer mortality for every county in the United States. (Mason and McKay, 1974; Hoover *et al.*, 1975). This '20-year county data' included sets of age-standardised rates, each of which was an average for the period 1950-1969, so that the published data allowed comparisons between places but not between times.

2.17 The early studies by Yiamouyiannis and Burk were based on the 20-year county data. Their results, which seemed to indicate higher cancer rates in fluoridated than in non-fluoridated localities, were initially reported briefly in National Health Federation handouts, in its Bulletin (Yiamouyiannis, 1975a, 1975b, 1975c) and in a publication called "Let's Live"; later versions appeared in a letter from Burk and Yiamouyiannis to Congressman J J Delaney which was written into the Congressional Record (Burk and Yiamouyiannis, 1975). (These studies are reviewed in Chapter 3 of this report).

2.18 The National Cancer Institute countered with short critical statements, issued in March and April 1975 (Hoover & Mason, 1975; Department of Health Education and Welfare, 1975) and then with their own studies, based largely on the same county data, which they reported as showing no adverse effect from fluoride or fluoridation. The Institute's studies were not published until late 1976 (Hoover *et al.*, 1976) but they had been issued informally, in preliminary form, in November 1975. It was these preliminary reports that the Royal College of Physicians was able to take into account in its review. (These NCI studies are discussed in Chapter 6).

2.19 Burk and Yiamouyiannis responded within a few weeks with a further letter to Congressman Delaney, again published in the Congressional Record (Yiamouyiannis & Burk, 1975). In their turn they criticised the NCI work but the main effect of their letter was to shift attention to another set of data and another form of study, around which the controversy has largely turned ever since. The data were the official year-by-year statistics for total numbers of cancer deaths in large American cities. The form of study was 'time-trend' analysis, already used for one of the NCI studies, in which the changes in cancer rates over time are compared in fluoridated and non-fluoridated localities. Yiamouyiannis and Burk selected for study ten fluoridated and ten non-fluoridated cities. ('The 20 US Cities'), most of which had featured in

their earlier studies, and primarily the same years, 1950 to 1969, as are covered by the 20-year county data. In the December letter they reported the first of four types of 'time-trend' study which they were to carry out using the 20 US cities data; in this one, 'crude' cancer rates (calculated from the numbers of all deaths from cancer and total populations for each city in each year) were shown to have risen faster in the fluoridated than in the non-fluoridated cities. (The study is discussed in Chapter 4).

2.20 The National Cancer Institute responded in turn, by analysing the same data (but for the census years only, and including 1970) using a routine technique known as 'indirect standardisation' (see Appendix 1) to allow for the effect of different demographic changes (i.e. changes in the age, sex and race structures) of the populations under study. The result, which contradicted the conclusions of Yiamouyiannis and Burk, was recorded in a letter dated February 6 1976 from the Director of the National Institutes of Health to Congressman Delaney. This letter was not published until late 1977, when it was included in Congressional Committee proceedings (Fredrickson, 1976). The NCI did not publish this analysis in the scientific press.

2.21 In the period from February 1976, three separate lines of investigation were pursued, each of them culminating in publications from 1977 onwards:
  (a) Three groups of scientists, two British and one American, analysed the 20 US cities data, with some variations of method or extensions of data covered, but all using the same basic technique as the National Cancer Institute. The results were all first published in 1977 (Doll and Kinlen, 1977; Oldham and Newell, 1977; Taves, 1977 and in National Academy of Sciences, 1977). The data used by the British groups had been transcribed for them by the NCI from routinely available American statistical publications; there were transcription errors in the data used and forwarded to Britain by the NCI and corrected results were later notified by the NCI and by the British researchers (Hoover, 1977; Kinlen and Doll, 1977; Oldham and Newell, 1979). The results, both before and after correction, were reported as showing no effect of fluoridation on cancer rates. (These studies are discussed in Chapter 5).
  (b) Two other American studies compared mortality in fluoridated and non-fluoridated localities but for a wider range of diseases, including cancer. Both studies covered a larger number of localities than the others mentioned above but the data overlapped substantially with the 20-city data. One study was a single-period comparison for many diseases (Erickson, 1978) and the other a further time-trend study (Rogot et al., 1978) on all causes of death combined as well as heart disease and cancer separately. Neither reported harmful effects from fluoridation. (These studies are discussed in Chapter 6).
  (c) Yiamouyiannis and Burk themselves responded to the Fredrickson letter (see 2.20) by seeking, from local health departments, more detailed data on cancer deaths in the 20 cities than are published in the official statistics. They used techniques different from those used by NCI to allow for the effect of demographic changes, including the technique of 'direct standardisation' (see Appendix 1) (Yiamouyiannis and Burk, 1977). It is on this paper that Yiamouyiannis and Burk have since principally based their claim that fluoridation increases cancer rates. The basic data are not generally available in the form used by them, and in no other studies have these data been examined, other than by derivation from the analyses reported by Yiamouyiannis and Burk (Maritz and Jarrett, 1983).

2.22 Although Yiamouyiannis and Burk (1977) had criticised the use of 'indirect standardisation' by the National Cancer Institute and other groups, Yiamouyiannis was soon to use it, with his own modifications. He claimed that his analysis confirmed a greater increase in cancer rates in the fluoridated cities. The results were at first reported briefly, in legal or committee reports (Yiamouyiannis 1977, 1978; Winner *et al.*, 1978), but details of Yiamouyiannis's modifications of the technique were circulated privately, somewhat later (Yiamouyiannis, 1980). All the Burk and Yiamouyiannis time-trend studies are discussed in Chapter 4.

2.23 Since 1978 dispute has continued, often in courts of law, on the relative merits of the different methods used for the analysis of the 20-city data. The analysis of straightforward data of this kind is a matter of routine all over the world. The extent of dispute that has arisen in this way over details of statistical method is therefore surprising. Recently, British workers have returned to the analysis of the 20-city and related data (Kinlen and Doll, 1981; Chilvers, 1982, 1983), with the prime intention of testing the effect, on the results of their analyses, of using the alternative statistical methods which are under dispute. They have reported that only certain of the differences of technique are of any practical importance. The results of the analyses are discussed in Chapter 5; the points of method which are of importance will be considered in detail in Chapters 4 and 5.

REACTIONS IN OTHER COUNTRIES: 1975-1979

2.24 In several other countries where fluoridation schemes were in operation analyses of official cancer mortality statistics in relation to fluordation were undertaken, within a short time of Yiamouyiannis and Burk making known their findings. Reports were published from Canada (Raman *et al.*, 1977; Wigle *et al.*, 1981), Australia (National Health and Medical Research Council (Australia), 1979; Richards and Ford, 1979), and New Zealand (Goodall *et al.*, 1980). None of the authors reported an association between fluoridation and cancer in the statistics of their country.

2.25 In two other countries small scale studies were carried out at around the same time on populations drinking naturally high-fluoride water. Binder (1977) from Austria, and Glattre and Wiese (1979) from Norway both reported somewhat lower cancer rates in the higher-fluoride areas.

2.26 All of the studies in this group are described in Chapter 8.

FURTHER STUDIES IN THE UNITED KINGDOM: 1979-1983

2.27 In the United Kingdom, studies had already been carried out and the report of the Royal College of Physicians published. No further studies were undertaken immediately in response to the Yiamouyiannis and Burk reports, although British scientists were active in the analysis of the American statistics. In 1979, however, Burk turned his attention to Britain. In September of that year he gave a paper at an Oxford conference (Burk, 1979a) in which he criticised Kinlen's analysis of cancer incidence data for fluoridated areas compared with nearby non-fluoridated areas (Kinlen, 1974, 1975). Burk claimed that a correct analysis showed an excess of cancer in fluoridated areas. In July 1980, Burk gave another paper to a conference in London, in which he drew attention to the trend of cancer deaths in Birmingham, England, following fluoridation, a trend which had originally been noted by Schatz and Schatz (1972) and subsequently by Brady (1977). He argued that it demonstrated a substantial excess of cancer deaths due to fluoridation. In reply, two papers (Cook-Mozaffari *et al.*, 1981; Cook-Mozaffari and Doll, 1981) criticised the accuracy and the methods of Burk's analysis and reported, on the basis of a standard form of analysis, that there

had been no disadvantage to Birmingham compared with other British cities, in terms of cancer mortality since fluoridation. The United Kingdom studies are considered in Chapter 7.

2.28 In September 1980 the Court of Session in Edinburgh began to hear a case seeking an 'interdict' (equivalent to an injunction in English law) that plans for fluordation in Strathclyde should be suspended. The case took nearly two years to hear; a considerable part of the case for the 'petitioner' (equivalent to plaintiff in English law) involved presentations by Yiamouyiannis and Burk of their own work. The judgement (Jauncey, 1983), in referring to the scientific issues, found that there was no evidence that fluoride at 1 ppm has an adverse effect upon health and, in particular,

(a) that no association between fluordation of water and increased cancer death rates in the consumers had been demonstrated;

(b) that no biochemical mechanism whereby fluoride at 1 ppm is likely to cause cancer or accelerate cancerous growth had been demonstrated; and

(c) that fluoride at 1 ppm is not mutagenic.

OFFICIAL REVIEWS OF FLUORIDATION AND CANCER

2.29 Proposals to introduce the fluoridation of water, and the continuation of existing fluoridation schemes, have been accompanied in many countries by official enquiries into the possible effects on health. The earliest publications of such an enquiry to include a review of the evidence relating to cancer was from New Zealand in 1957. There have been some sixteen further publication of this nature, from Australia, Canada, Norway, South Africa, Sweden, the United Kingdom and the United States. None of them has concluded that fluoridation causes cancer.

2.30 The World Health Organisation has published three reviews of the issue. The earliest was in 1958; this was only able to consider cancer briefly, but the later reviews in 1982 and 1983 were comprehensive. All have agreed in concluding that "variations geographically and in time in the fluoride content of water supplies provide no evidence of an association between fluoride ingestion and mortality from cancer in humans" (IARC, 1982). The World Health Assembly has passed several resolutions in support of fluoridation of water (e.g. Resolutions WHA 22.30 (1969), 28.64 (1975), 31.50 (1978)).

2.31 A list of the various reviews is appended to this report. (Appendix 4).

SUMMARY OF THE HISTORY

2.32 The pivot of the fluoridation and cancer debate was the series of analyses of cancer mortality statistics of large fluoridated cities in the United States, carried out by Yiamouyiannis and Burk between 1975 and 1979. Few substantial studies were published before that time. The most important were studies of a range of diseases in communitites which had been supplied with naturally high-fluoride waters over a long period. The Yiamouyiannis and Burk studies, however, were followed within a short period by analyses of cancer mortality statistics of many fluoridated communities; those from the United States and the United Kingdom were based initially on substantially the same data as the reports by Yiamouyiannis and Burk. It is worth noting that they were all carried out from, or in close association with, highly reputed professional or official health organisations; the cancer and fluoridation hypothesis appears to have elicited little concern among medical scientists in general.

2.33 The Yiamouyiannis and Burk claim depends on the assertion that their own methods of analysis are to be preferred to the standard methods used by others. It is for this reason that in this report the detailed consideration of the evidence begins with the studies of Burk and Yiamouyiannis and pays close attention to their methods. The early studies are discussed in Chapter 3, and the later series of time-trend studies in Chapter 4.

CHAPTER 3

THE AMERICAN STUDIES OF YIAMOUYIANNIS AND BURK — (A) COMPARISON OF CANCER RATES FOR A SINGLE PERIOD IN FLUORDIATED AND NON-FLUORIDATED AREAS

INTRODUCTION

3.1 The hypothesis that fluoridaion increases cancer deaths rates was examined by Yiamouyiannis and Burk initially on the basis of a series of simple comparisons of cancer death rates for different areas in the United States. Although these authors' later analyses of trends in such rates over time, to be discussed in Chapter 4, extended and superseded the earlier work, it is nevertheless helpful to examine the basis of the original claims.

THE DATA

3.2 With one exception (see para 3.19 below), the data used for the early work were drawn from the publication by Mason and McKay (1974), which presents the numbers of cancer deaths and the age-standardised cancer death rates for each county of the United States, for the period 1950-1969. The numbers of deaths and the death rates are classified in that publication by the site of cancer, sex and race (whites and non-whites), but the data are pooled for the 20-year period. Thus, for example, the total number of deaths from cancer of the stomach in white males in Philadelphia county over the period 1950-1969 is given as 3157, and the corresponding average annual age-adjusted death rate is 19.5 per 100,000 per year.

3.3 Fluoridation data were obtained by the authors from an official report (Department of Health, Education and Welfare, 1970). Only deliberate fluoridation was being considered by them, rather than differences in naturally-occurring levels of fluoride. The fluoridation schemes in all of the fluoridated cities in these studies commenced after 1950, i.e. during, rather then before, the period for which death rates were being examined.

3.4 In most of these studies, the cancer death rates for <u>counties</u> were grouped according to the fluoridation status of the major <u>city</u> within the county (Yiamouyiannis, 1975a, 1975b, 1975d; Burk and Yiamouyiannis, 1975), although the fluoridated cities selected for one study were coterminous with counties (Burk and Yiamouyiannis 1975). In another study, cancer mortality data for the cities themselves were apparently used for both fluoridated and non-fluoridated cities (Yiamouyiannis and Burk, 1977).

3.5 The sets of cities dealt with in the several reports which are discussed in this Chapter are not independent, but overlap, often considerably. The studies therefore represent several approaches to the examination of related sets of data.

3.6 Yiamouyiannis and Burk gave most attention to death rates for cancers of all sites combined, but death rates for cancers of individual sites were also explored (Yiamouyiannis, 1975d; Burk and Yiamouyiannis, 1975). It is convenient to discuss the studies in these two classes separately.

**CANCER DEATH
RATES-ALL SITES
COMBINED**

Methods and Results

3.7 Yiamouyiannis (1975a) first examined age-standardised death rates from cancers of all sites combined, in white males only. The comparison was based on the eight cities with populations of over one million in 1960. Rates for the counties containing the six cities which had fluoridated by 1969 were compared with those for the counties containing the two non-fluoridated cities. The cities referred to in this first comparison are listed in Table 3.1.

Table 3.1 Cities in the first comparison

Fluoridated Cities (year of initial fluoridation)		Non-fluoridated cities
Baltimore	(1952)	Los Angeles
Philadelphia	(1954)	Houston
Cleveland	(1956)	
Chicago	(1956)	
New York	(1965)	
Detroit	(1967)	

3.8 For the counties containing the six fluoridated cities, the age-standardised cancer death rate for white males ranged from 18 per cent to 34 per cent above the national average. Of the two non-fluoridated counties, the rate for Los Angeles county was the same as the national average, while that for Houston county was 27 per cent below. Yiamouyiannis urged that therefore fluoridation should cease.

3.9 An error in this comparison was subsequently corrected by Yiamouyiannis (1975b). The Houston county rate had been used in relation to Houston city (one of the non-fluoridated cities), but Houston city is in Harris county. The relevant cancer death rate for Harris county was 8 per cent above the national average.

3.10 In a second comparison, the selection of cities was expanded (Yiamouyiannis, 1975d) to the ten largest fluoridated cities and the ten largest non-fluoridated cities. They are listed in Table 3.2.

Table 3.2 Cities in the second comparison

Fluoridated Cities (year of initial fluoridation)		Non-fluoridated cities
Washington D.C.	(1952)	Los Angeles
San Francisco	(1952)	Houston
Baltimore	(1952)	San Antonio
Milwaukee	(1953)	San Diego
Philadelphia	(1954)	Seattle
St Louis	(1955)	Memphis
Cleveland	(1956)	Atlanta
Chicago	(1956)	Boston
New York	(1965)	New Orleans
Detroit	(1967)	Cincinnati

3.11 On average, the cancer death rate for white males in the counties containing these ten fluoridated cities was 23 per cent above the national average, the corresponding figure for the counties containing the ten non-fluoridated cities being only 10 per cent above the national average. However, the ranges of the individual county rates in the two groups overlapped considerably, the excess of the rates for counties containing three of the non-fluoridated cities, namely Boston (28 per cent), New Orleans (32 per cent) and Cincinnati (17 per cent), being within the range for the fluoridated group (17 to 34 per cent).

3.12 For a third comparison, Yiamouyiannis (1975d) made two changes to his selection of cities (see Table 3.3). He described the three non-fluoridated cities noted above as "aberrant", and excluded them on the grounds that their high cancer death rates had "already been linked to other waterborne contaminents". In their place, the three next largest non-fluoridated cities (Kansas City, Columbus and Phoenix) were substituted. The second change was the exclusion, from the flouridated group, of New York and Detriot, where fluoridation had not begun until the 1960s. They were replaced by Pittsburgh (fluoridated 1953-58) and Buffalo (fluoridated 1955).

Table 3.3 Cities in the third comparison

Fluoridated Cities (year of initial fluoridation)		Non-fluoridated cities
Washington D.C.	(1952)	Los Angeles
San Francisco	(1952)	Houston
Baltimore	(1952)	San Antonio
Milwaukee	(1953)	San Diego
Pittsburgh	(1953-8)	Seattle
Philadelphia	(1954)	Memphis
St Louis	(1955)	Atlanta
Buffalo	(1955)	Kansas City (Missouri)
Cleveland	(1956)	Columbus
Chicago	(1956)	Phoenix

3.13 The average age-standardised cancer death rate for white males in the counties containing the fluoridated cities was now 22 per cent above the national average, while that for the counties containing the non-fluroidated cities was now only 2 per cent above the national average. The exclusion of the "aberrant" non-fluoridated cities had increased the difference between the average rates in the two groups of counties, making the comparison between the two groups more adverse with respect to the counties containing the fluoridated cities.

3.14 All of the comparisons so far had grouped the county mortality rates according to the fluoridation status of the major city in the county. To reduce the uncertainties arising from the use of county mortality data, the comparisons in a further report were limited to the six large fluoridated cities for which the cancer death rates for the cities themselves were available (Burk and Yiamouyiannis, 1975). Five of the six had appeared in the earlier groups of ten fluoridated cities, but one (Denver) was a new addition.

3.15 The non-fluoridated cities in the fourth comparison were the six largest from the original group of ten non-fluoridated cities. County mortality rates were used in this part of the calculation; unlike the fluoridated cities used in this study, the non-fluoridated cities were not necessarily coterminous with the counties, and therefore the city rates were not necessarily the same as the county rates. The choice of cities was made without reference to their mortality rates, and therefore two of the "aberrant" non-fluoridated cities were reinstated in this group. The cities included in the comparison are listed below (Table 3.4).

Table 3.4 Cities in the fourth comparison

Fluoridated Cities (year of initial fluoridation)		Non-fluoridated cities
Washington D.C.	(1952)	Los Angeles
San Francisco	(1952)	Houston
Baltimore	(1952)	San Antonio
Denver	(1954)	San Diego
Philadelphia	(1954)	Boston
St Louis	(1955)	New Orleans

3.16 The previous studies had been limited to mortality rates for white males only, but in this fourth comparison Burk and Yiamouyiannis combined the age-standardised death rates for cancer (all sites together) for all four population categories, namely white males, white females, non-white males and non-white females. They stated that, for each group of cities, they "weighted the mortality rates for each of these categories in accordance with the actual number of deaths involved per category, to yield the total number of cancer deaths per given city. Then the total number of deaths were weighted according to the total city population, to yield, finally, the total number of cancer deaths in the entire group of six cities, which, divided by the total population of the six cities yielded the fully weighted average mortality rate". (Burk and Yiamouyiannis, 1975).

3.17 The result of the calculations was a figure of 188 cancer deaths per year per 100,000 population for the fluoridated cities, the corresponding figure for the counties containing the non-fluoridated cities being only 163. Burk and Yiamouyiannis multiplied the excess rate of 25 deaths per year per 100,000 population, in the flouridated cities, by 90 million (the total fluoridated population of the United States) to estimate that there were "some 22,500 excess deaths in the United States per year linked with imposed fluoridation".

3.18 For the fifth comparison, the authors (Burk and Yiamouyiannis, 1975) selected three of the above fluoridated cities (San Francisco, St Louis, and Denver) and, for each of them, compared the age-standardised mortality rates for cancers in all sites combined, for white males only, with the corresponding mortality rates in a selection of adjacent county areas centred on non-fluoridated cities. In each case, the rate for the fluoridated city was higher than the average for the non-fluoridated group by 15-21%.

3.19 A sixth comparison was mentioned briefly in a later paper (Yiamouyiannis and Burk, 1977). Cancer death rates (presumably for all sites combined) for fluoridated and non-fluoridated cities east of the Mississippi with populations of 10,000 or over were compared State by State. An overall figure, derived by use of a weighting procedure, was interpreted as indicating as excess in cancer death rate in the fluoridated cities. No details were given, and the matter does not appear to have been pursued further.

Comments of the Working Party

3.20 The main problem in interpreting the results from simple comparisons of cancer mortality in different areas is whether the groups being considered are similar enough to bear comparison one with another. If the groups differ in features other than fluoridation status, then it would be necessary to ask whether any of those features provide a more likely explanation of the observed differences in cancer mortality. The fluoridated cities chosen by Yiamouyiannis and Burk tended to be situated towards the east of the country and to be older-established than the non-fluoridated cities. They are likely to have differed from the non-fluoridated cities with respect to very many social and economic factors, some of which are relevant to the risk of cancer. This is sufficient to indicate that it was not reasonable to claim that fluoridation causes cancer, on the basis of mortality data from these sets of cities (or the counties containing them), unless other possibly relevant differences between the fluoridated and non-fluoridated areas had been taken into consideration. The need for caution when comparing vital statistics for non-matched communities is well established, but Yiamouyiannis and Burk neglected this in each of the six analyses described above, and even claimed that "it is not likely that these excess mortality values will be reduced to anywhere near insignificance by any attempt to rule them out on bases of

'social status', ethnic composition, sex, climate, other carcinogens conceivably introduced into the water supplies, and many other possibilities''. They were, however, not comparing like with like, and their results should have been regarded only as possible grounds for further study, and not as grounds for drawing firm conclusions.

3.21 The interpretation of the results of these studies is complicated by the use of county mortality rates in relation to city fluoridation status, as most of the cities under study form only a part of the relevant county (for example, the non-fluoridated cities in Table 3.4 contained only 74 per cent of the county population). If the county rate is not an accurate reflection of the city rate, or if the fluoridation status of the city is not a good index of the fluoridation status of the county, the procedure is not valid. Only the sixth comparison (para 3.19) appears to have used both fluoridation data and mortality data for cities throughout, although the brief description given by the authors lacks these details.

3.22 The exclusion, from the third comparison (para 3.12), of the three ''aberrant'' non-fluoridated cities with the highest cancer rates represents an unjustified selection from amongst the data. Yiamouyiannis argued that the higher cancer death rates of these cities ''had already been linked to other waterborne contaminants'', but this is no more than a tentative hypothesis which has not been scientifically established despite extensive research. Although he appears to have accepted this hypothesis as an explanation for the high mortality rates in three non-fluoridated cities, Yiamouyiannis nowhere indicated that he had made any attempt to explore whether ''other waterborne contaminants'' could be responsible for the similar high mortality rates in the fluoridated cities. It is clear that the exclusion of three ''aberrant'' cities has no adequate basis; it is an example of a well-recognised error of method which is certain to alter the results in the direction of the hypothesis supported by Yiamouyiannis.

3.23 The methods used by Yiamouyiannis and Burk to combine mortality rates in two of these studies are unconventional and produce summary figures which are suspect. The fully-weighted average mortality rate calculated by these authors in their fourth comparison (para 3.16) employs, at the first stage, the number of deaths in each group to weight the mortality rated for that group. This is an entirely unsound procedure which gives additional weight to those sub-group rates which are already relatively high. Using conventional direct standardisation procedures we have shown that the method employed by Yiamouyiannis and Burk exaggerated the difference between the cancer mortality in the fluoridated and non-fluoridated areas by a factor of more than 1½. Rather than using a well-established procedure these authors devised a novel one which had the effect of shifting the results in the direction of the hypothesis they favoured. The weighting procedure employed in the study of cities east of the Mississippi is also unconventional and not validated but the details which would allow the analysis to be checked were not published; it is therefore impossible to interpret the results.

3.24 The estimate by Burk and Yiamouyiannis of the number of excess deaths in the United States per year linked with fluoridation, which is based on their fourth comparison, is meaningless. It assumes firstly that the summary figures discussed above are valid, secondly that the difference between the summary figures represents an effect of fluoridation, and thirdly, that the populations studied are representative of the whole United States population. The authors did not demonstrate that any of these assumptions is correct.

3.25 Altogether these authors seem to have been prepared to consider seriously only one explanation of the differences in the cancer rates which they have examined. The crucial defect of all six comparisons of mortality from all cancers combined is their failure to compare 'like with like', coupled with the absence of any attempt to explore whether this alone could account for the differences in cancer rates. Instead, Yiamouyiannis and Burk have been led to select and analyse their data in ways which best accommodate their hypothesis of harm from fluoridation.

CANCER DEATH RATES — SPECIFIC SITES OF CANCER

Methods and Results

3.26 Age-standardised death rates for cancers of individual sites were considered in two of the publications cited above. Yiamouyiannis (1975d) explored these rates in the counties containing the ten largest cities fluoridated before 1960, and the counties containing the ten largest non-fluoridated cities, excluding the "aberrant" cities, with high cancer death rates (see Table 3.3 above). He noted that the average age-standardised death rate for each of seven sites of cancer in white males (tongue and mouth, oesophagus, stomach, large intestine, rectum, kidney, bladder and urinary organs) and for each of two sites of cancer in white females (ovary and fallopian tube, breast) was higher in the counties containing the fluoridated cities. He calculated that "about 90 per cent of the increased cancer death rate in fluoridated cities vs non-fluoridated cities" was due to those cancers.

3.27 In a further comparison of site-specific data, the "aberrant" cities were restored to the non-fluoridated group (Burk and Yiamouyiannis, 1975). The cities involved were therefore the fluoridated cities in Table 3.3 and the non-fluoridated cities in Table 3.2. The cancer mortality rates for the above nine site/sex/race categories were added together for each county, and an unweighted average rate was derived for each of the two groups of counties, fluoridated and non-fluoridated. This led to an estimated excess death rate, for those selected categories, of 24.5 per 100,000 in the fluoridated group. The estimated excess death rate was multiplied by the total fluoridated population of the United States to give an estimated 22,500 excess deaths per year, agreeing with the previous estimate noted in paragraph 3.17 above.

Comments of the Working Party

3.28 These studies share many of the defects of the comparisons for all sites. Thus they suffer from the failure of Burk and Yiamouyiannis to show that the fluoridated and non-fluoridated areas were otherwise similar, or to consider whether or not social and environmental differences between the two groups could account for the observed differences in mortality rates, and from the uncertainty introduced by the use of county rates as a substitute for city rates. Furthermore they suffer from the choice of the group of non-fluoridated cities, in one comparison, in such a way as to exclude those counties whose higher cancer death rates would not lend support to their hypothesis.

3.29 In addition, the methods used by Burk and Yiamouyiannis (1975) to estimate excess cancer mortality from the site/sex/race specific data are inadmissible. Firstly, they involve the addition of rates for males and females without any adjustment of the denominator, a procedure which will inevitably roughly double the difference between the average rates for the fluoridated and non-fluoridated areas. Secondly, they apply a rate for whites only to the entire population. The authors attempted to justify their procedures by claiming that the rates for sex/race groups were not very different from one another, and they promised to publish further details (Burk and Yiamouyiannis, 1975). Such details did not appear.

37

3.30 The authors do not seem to have considered whether the pattern of results might have arisen by chance. Yiamouyiannis (1975d) suggested that the pattern of cancers which were apparently adversely affected by fluoridation of water accorded with what would be expected on theoretical grounds, but these grounds were advanced in response to the data and would have required independent confirmation. That has not since been forthcoming; indeed subsequently these authors said that "Trend data regarding death rates in specific sites .... indicate less of a tissue specificity than that previously reported ..." (Yiamouyiannis and Burk, 1975). Furthermore some of the reasons advanced by Yiamouyiannis were very speculative. For example, in relation to an excess of breast cancer, he suggested that since breast milk is low in fluoride "there must be areas in the breast in which fluoride is concentrated". He offered no evidence in support of this proposition; as with the hypothesis of cancer caused by waterborne contaminants (see para 3.22), this is an example of one unsupported hypothesis being used to bolster another. In fact, as the levels of fluoride in blood plasma and in milk are similar, there is no reason to postulate the existence in the breast of areas which concentrate fluoride.

DISCUSSION OF STUDIES CONSIDERED IN CHAPTER THREE

3.31 Serious defects in the technique of every one of the comparisons considered in this chapter have already been indicated. These technical and logical defects of detail are not, however, critical to the conclusions which may be reached. It is the limitation of the basic method of simple comparisons of rates, without account being taken of the varying character of the places being studied, which chiefly determines our conclusion.

3.32 In spite of their defects these studies had the advantage of being based on reliable data which take account of demographic factors. They did show that certain age-adjusted cancer mortality rates, aggregated over 1950-69, were higher in some counties containing large fluoridated cities than in some counties containing large non-fluoridated cities. Such evidence was enough only to suggest a line of investigation. Other explanations of the differences in rates should have been considered and further studies carried out before a conclusion was reached. Burk and Yiamouyiannis (1975) acknowledged the possibility of some error but doubted whether a difference of the order they indicated could be explained other than as an effect of fluoridation; they urged people to place the simplest interpretation on their findings and to act on them in isolation. However, extensive experience of cancer epidemiology shows that differences of the order reported are commonly found in such limited comparisons, often without immediately apparent reason, and that the simplest and most likely explanation of such a finding in such a basic study is that it was a consequence of the dissimilarity of the populations studied. Public conclusions were certainly not justified; further study may have been.

3.33 Several ways were available by which the question of whether or not fluoridation causes cancer could have been investigated further. Whatever epidemiological methods are chosen in such a situation it is essential that cancer rates in several sets of fluoridated and non-fluoridated populations should be examined to establish whether there is a consistent difference. At first sight, it may seem that Yiamouyiannis and Burk have already done so in this series of studies, but inspection of Tables 3.1 to 3.4 revels that the groups of cities chosen overlapped very considerably. The data were not independent, and it is therefore not surprising that the results of the studies were similar.

3.34 Two types of investigation were possible, using the available mortality data. One was the study of the differences in rates in such a way as to take

account of the differences in social and economic factors in the communities studied; some useful studies of this kind were undertaken by other authors and are considered in Chapter 6. An alternative was the study of the trends in cancer mortality in communities in relation to fluoridation. The analyses of this nature by Yiamouyiannis and Burk, which were apparently undertaken in response to criticism of the studies we have just considered, are the subject of the next chapter.

CONCLUSION TO CHAPTER THREE

3.35 The simple comparisons of age-adjusted mortality rates connected with various groupings of US cities do no more than suggest a hypothesis for further study. They do not provide reliable evidence that fluoridation causes cancer.

CHAPTER 4

THE AMERICAN STUDIES OF YIAMOUYIANNIS AND BURK — (B) STUDIES OF TRENDS IN CANCER RATES IN RELATION TO FLUORIDATION OF WATER

INTRODUCTION

4.1 The time-trend studies of Yiamouyiannis and Burk were based on a comparison of the trends in cancer mortality rates in two sets of cities, a fluoridated set and a non-fluoridated set. The aim of these studies was to examine not whether the cancer mortality rates of the two sets of cities were simply different, but whether the change in rates over time appeared to have been influenced in the set of fluoridated cities by the introduction and practice of fluoridation. Cancer mortality was observed over an extended period, from 1940 to 1969 in the first of the studies, and from the early 1950s to 1968 or 1969 in subsequent studies. These periods encompassed the shorter period of 1952 to 1956 during which fluoridation was initiated in the ten cities in the fluoridated set.

4.2 The fluoridated set consisted of the ten largest cities in the United States which had commenced fluoridation before 1960 (see Table 4.1). With one additional condition the non-fluoridated set consisted of the ten largest cities in the United States not fluoridated up to 1969. The further condition required that each of the non-fluoridated cities had a crude cancer death rate in 1953 of over 155 per 100,000, in order to match the minimum value observed among the fluoridated set. As a result the three "aberrant" non-fluoridated cities Boston, New Orleans and Cincinnati, excluded in some earlier studies (see para 3.12 above), were reinstated, but five otherwise suitable non-fluoridated cities (Houston, San Antonio, San Diego, Memphis, Phoenix) were now excluded.

Table 4.1 Cities selected for comparison by Yiamouyiannis and Burk (1977).

Fluoridated Cities (date of initial fluoridation)		Non-fluoridated cities
Washington D.C.	(1952)	Los Angeles
San Francisco	(1952)	Boston
Baltimore	(1952)	New Orleans
Pittsburgh	(1952)	Seattle
Milwaukee	(1953)	Cincinnati
Philadelphia	(1954)	Atlanta
St Louis	(1955)	Kansas City (Missouri)
Buffalo	(1955)	Columbus
Cleveland	(1956)	Newark
Chicago	(1956)	Portland

4.3 Cities, rather than other geographical areas, were chosen for these studies because they tend to be fluoridated in their entirety, or not at all. One disadvantage, however, is that the official United States cancer statistics for cities (published in the annual volumes of 'Vital Statistics of the United States') give only limited information. Total numbers of deaths (i.e. for men and women of all ages) are available for the combination of cancers of all sites,

and for a limited range of body sites over a restricted period. For some of their analyses, therefore, Yiamouyiannis and Burk obtained more detailed, usually unpublished, information from local health departments.

4.4 These studies extend the earlier studies discussed in Chapter 3 above, and provide virtually the sole epidemiological basis for the claim that fluoridation increases cancer rates. It is this which necessitates their close and detailed examination here. Much of the data, and many details of the methods used in the analyses, are unpublished, but some have been made available to the Department of Health and Social Security by the authors directly, or as a result of a court case (McColl vs Strathclyde Regional Council) (Jauncey, 1983). The Working Party has therefore been able to carry out fuller checks than were previously possible. It wishes to record its gratitude for all the assistance which it has received.

4.5 The different sources of mortality data used by Yiamouyiannis and Burk permitted them to undertake several types of analysis, whose bases for comparison fall into four categories:

    i) Crude cancer death rates for whole populations.

    ii) Cancer death rates in subgroups of the population: age-specific rates.

    iii) Cancer death rates directly standardised for age.

    iv) Cancer death rates indirectly standardised for age, race and sex.

Each of the following four sections of this chapter, corresponding to the four categories, follows a common pattern. The details of the methods used are followed by the results of the analysis, and the authors' conclusions; we then comment on the analyses, making reference where necessary to studies by other authors. We draw the discussion of all of these studies to a conclusion in the final two sections of the chapter.

CRUDE CANCER DEATH RATES FOR WHOLE POPULATIONS

Data and Calculations

4.6 The basic data for the principal analysis in this group consisted of the total numbers of deaths from cancer at all body-sites, for men and women of all ages and races together. The calculation of the death rates by Yiamouyiannis and Burk involved four stages:

    i) The numbers of cancer deaths for each city for each year from 1940-50 and 1953-69 inclusive were obtained from successive volumes of 'Vital Statistics of the United States'. Data had not been published for the intermediate years 1951 and 1952, which were therefore omitted from the analysis. Data were also unavailable for Boston (one of the non-fluoridated cities) for 1953-54 and 1956-58, and the numbers of deaths for those years were estimated by linear interpolation (that is, by assuming that cancer deaths in Boston increased regularly each year).

    ii) The population of each city was obtained from the official census reports of 1940, 1950, 1960 and 1970. The size of the populations for each of the intermediate years was estimated by linear interpolation (that is, by assuming that, for any given city, the population increased regularly).

    iii) Crude cancer death rates were then calculated for each city for each year, by dividing the number (or estimated number) of deaths by the total enumerated (or estimated) population.

    iv) For each year, the calculated crude rates for the ten fluoridated cities were added together, and then divided by the number of these cities; the procedure was repeated for the non-fluoridated cities. This procedure results in an unweighted (equally weighted) average of the rates for the individual cities. It contrasts with a rate calculated simply by dividing

the total number of deaths in the ten fluoridated cities, say, by the total number of people in them: a method which, in effect, gives greater weight to the rates in large cities.

Presentation and Interpretation

4.7 The numerical results of this analysis have appeared only in a letter read into the United States Congressional Record (Yiamouyiannis and Burk, 1975), but graphical representations of the trends have been presented in several places (Burk, 1976; Yiamouyiannis, 1977; Yiamouyiannis and Burk, 1977; Yiamouyiannis, 1980; Graham and Burk, 1984) with somewhat differing choices of fitted curve. One of the versions is reproduced in figure 1. The calculations on which it is based have been repeated for the Working Party, referring to the original data sources, with essentially identical results (Chilvers, 1983).

Figure 1 Annual average crude cancer mortality rates in fluoridated and nonfluoridated cities, 1940 — 1969
(Yiamouyiannis and Burk, 1977)
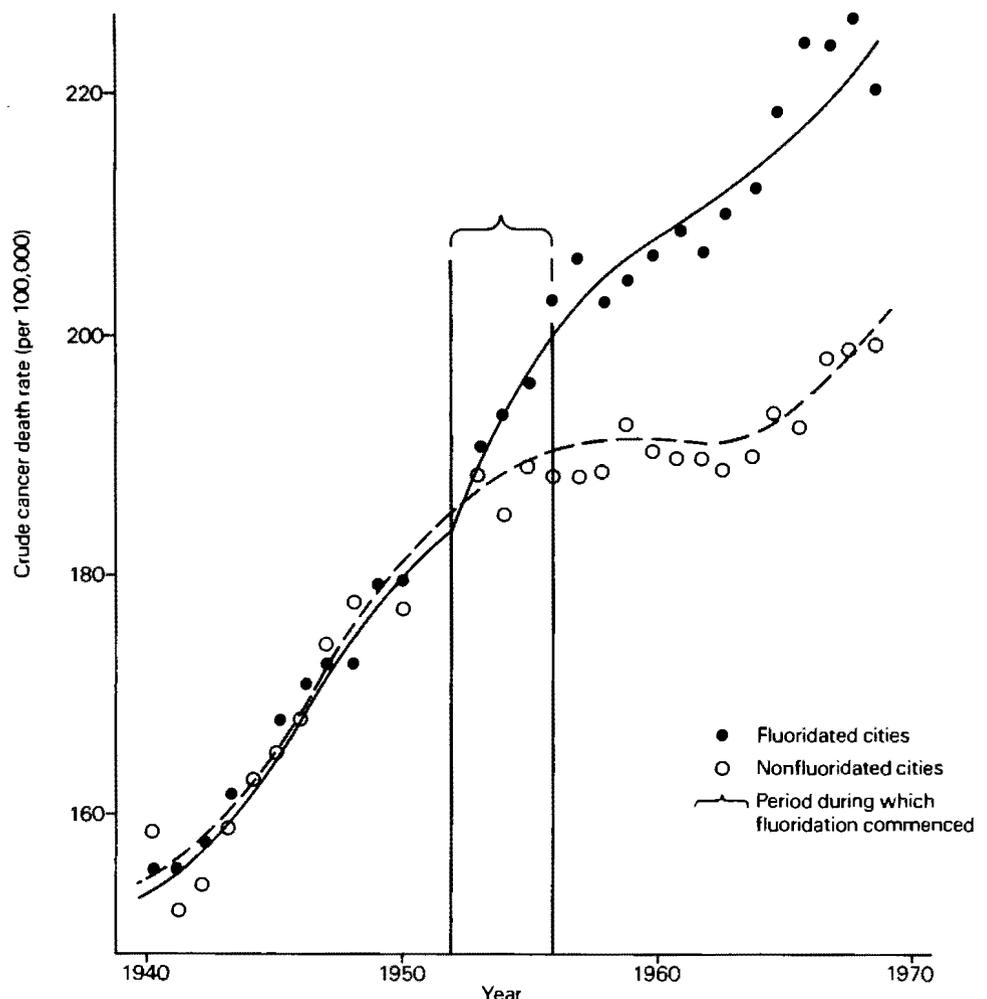
4.8 Yiamouyiannis and Burk (1977) pointed out that "the crude cancer death rates of both groups of cities had a strikingly similar trend between 1940 and 1950. Subsequent to fluoridation, however, an equally striking divergence could be observed ....". They concluded that the divergence represented a "prompt and increasing linkage of fluoridation with excess cancer deaths as a function of time" (Burk and Yiamouyiannis, 1976).

4.9 In subsequent presentations, Burk (1979b, 1980, 1981) calculated the differences between the averaged crude cancer death rates (fluoridated cities less non-fluoridated cities) for each successive year—a difference which he called the Δ CDR*. Between 1940 and 1952, the Δ CDR decreased slightly, and after 1952 it increased. This much is apparent from the rates for the two groups, as illustrated in Figure 1. Burk proceeded to calculate the trend over the years from and including 1953 (the first year following the initial fluoridation in these cities), repeating the calculation for different numbers of years (i.e. 1953-5, 1953-6 etc). The greatest average annual increase in Δ CDR was over the five-year period from 1953 to 1957. Burk decided that this was the most appropriate estimate of the trend; he stated that he was "looking for an abrupt change linked with fluoridation", and inferred that this was the most suitable method to reveal "the prompt and abrupt action of artificial fluoridation on human cancer mortality" (Burk, 1981).

4.10 A subsidiary analysis in the original paper (Yiamouyiannis and Burk, 1977) was based on the numbers of deaths from three separate groups of cancers, namely respiratory, digestive, and 'other'. The trends in crude rates for the period 1952-70, for the two sets of cities, were represented by straight lines fitted to the annual average rates for the three groups of cancers. The crude death rates for respiratory cancers, and for 'other' cancers, were shown to be increasing more in the fluoridated than in the non-fluoridated cities. For digestive tract cancers, the rates decreased in both sets, but the decrease was greater in the non-fluoridated cities. No conclusion was drawn from this analysis.

Comments of the Working Party

4.11 Crude death rates could provide a suitable basis for comparison of trends only if there had been no demographic or other changes (apart from fluoridation) in the two sets of cities, which could have influenced cancer death rates. It is however known that different age groups, sexes and races within the United States population exhibited different cancer rates irrespective of fluoridation, (Fig. 2) and it has since been shown that the demographic structures of the fluoridated and non-fluoridated cities have altered in different ways (see paras 5.5 and 5.9). Yiamouyiannis and Burk's conclusion is therefore based on an inappropriate comparison; they did not compare like with like.

4.12 Burk has argued that the similarity of the crude rates in the two sets of cities in the pre-fluoridated period 1940-50 "provides the best possible control for events taking place after fluoridation" (Burk, 1979b). This is clearly a false argument: the crude cancer death rates prior to 1950 have no influence on demographic or other changes for the years 1953-69. Burk's contention that the use of such a "control" makes demographic standardisation unnecessary is unjustifiable. His analysis of the differential crude death rate (Δ CDR) is similarly invalid.

4.13 The most simple interpretation of the crude rates (ignoring for a moment the essential requirement for demographic standardisation) would not in fact necessarily be that there was an effect of fluoridation. The divergence after 1952 did not result from an accelerated increase in the cancer death rates in the fluoridated cities, (as would be expected if fluoridation were a major influence on cancer death rates), but from a retardation of the increase in the non-fluoridated cities. This was confirmed when the trends in crude

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*Δ CDR = delta cancer death rate. Burk has used the same term to mean the difference between the average trends in cancer death rates after and before a given year, for a given city (see paragraph 7.19).

cancer death rates in <u>individual</u> cities were examined for the Working Party. In only three of the ten fluoridated cities was there any change in trend following fluoridation; in those three, the changes were in different directions and at different times after fluoridation (Chilvers, 1983).

Figure 2 Death rates for malignant neoplasms, USA 1950
(Data from Oldham and Newell, 1977)
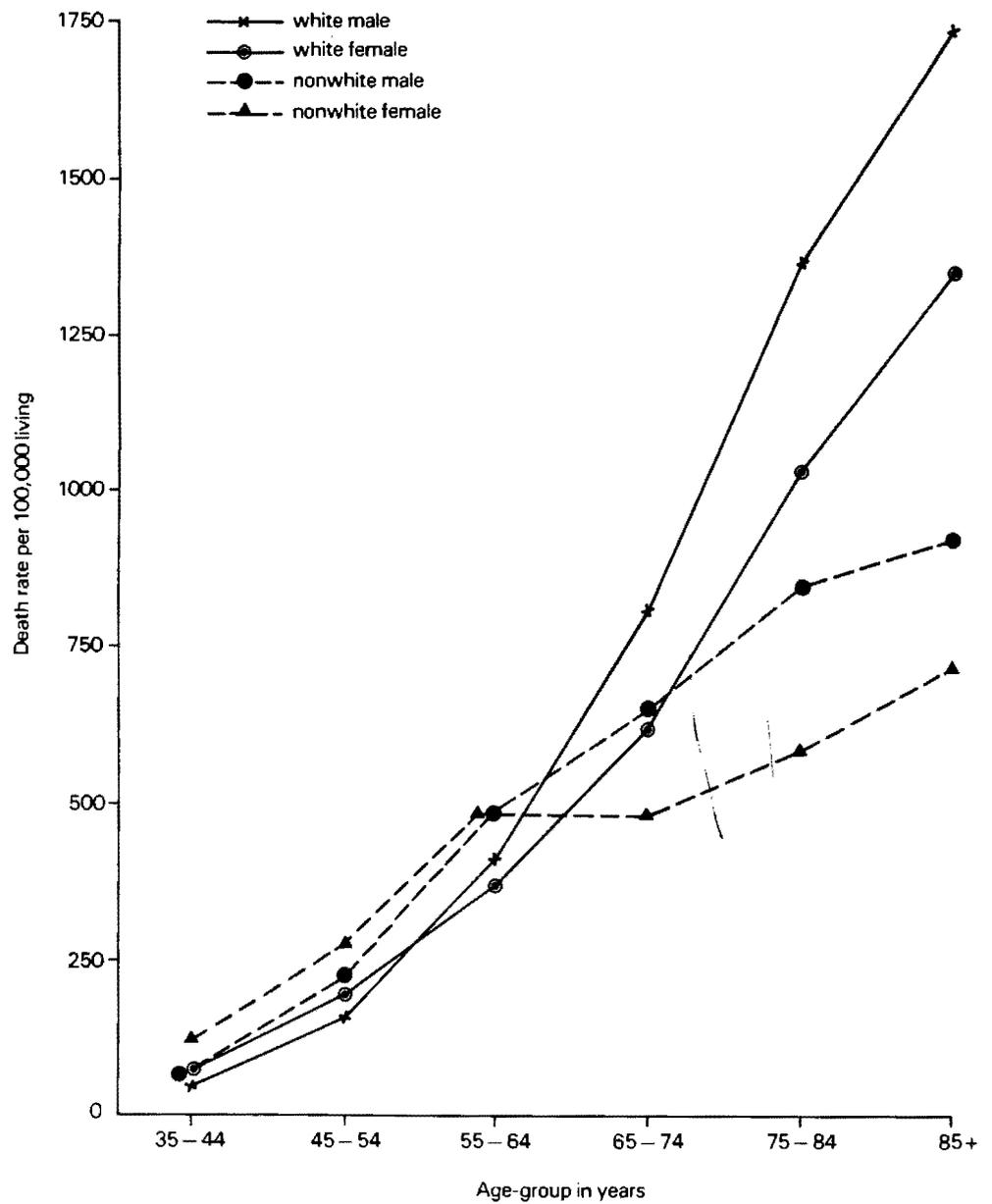
CANCER DEATH RATES IN SUB-GROUPS OF THE POPULATION: AGE SPECIFIC RATES

Data and Calculations

4.14 Yiamouyiannis and Burk (1977) acknowledged that cancer death rates are influenced by the age distribution of a population (that is, the proportion of the population at each age), and that there was a more rapid increase in the proportion of older people in the population of the fluoridated than the non-fluoridated set of cities from 1950 to 1970. They therefore compared trends in cancer death rates in the two sets of cities for four broad age-groups (0-24, 25-44, 45-64, 65+) over the post-fluoridaton period 1952-69. They could only use broad age-groups because the data, which they had obtained from local health departments, did not allow further sub-division. The calculations involved the following stages:

i) The numbers of cancer deaths for each year among the residents of each city, for men and women of all races together, and from cancers of all body sites together, were obtained from state and city health departments. The deaths were assigned to the four broad age-groups indicated above.

ii) The number of people in each age-group in each city was obtained from the census reports for 1950, 1960 and 1970. The size of the populations for each of the intermediate years, and for each of the four age-groups, was estimated by linear interpolation.

iii) The age-specific cancer death rates were then calculated for each of the four age-groups in each city in each year, by dividing the number of deaths in each age-group by the appropriate enumerated (or estimated) population for that group.

iv) For each age-group in each set of ten cities (fluoridated or non-fluoridated), the trend in age-specific cancer death rate was calculated by the technique of linear regression, in two ways:

   a) starting with the age-specific cancer death rate in each of the ten cities for each year, or

   b) starting with the average age-specific death rate for that set of ten cities for each year. This average was unweighted, that is, it was calculated by adding the rates for the ten cities, and dividing by ten.

The two methods a) and b), are algebraically equivalent.

v) The gradients of the resulting trend-lines represented the average annual increase in the age-specific cancer death rate. The gradients for the two sets of cities were compared, for each age-group, by estimating the cancer death rates for 1952 and 1969 from the trend lines and comparing the 1952-1969 increases. Two different sets of results arose from the two methods of calculation of trend described in iv).

vi) Alternatively, for each age-group, the unweighted average age-specific cancer death rate for the set of non-fluoridated cities for a particular year was subtracted from the corresponding rate for the set of fluoridated cities. The procedure was repeated for each year, and the trend in these differences of average age-specific cancer death rates was calculated by linear regression. A third set of results arose from this method.

Presentation and Interpretation

4.15 Yiamouyiannis and Burk claimed that the cancer death rate had increased more rapidly in the fluoridated cities, but only in the two older age-groups. For the 45-64 age group, their results indicated that the cancer death rate had increased in the fluoridated set by approximately 17 per 100,000 population more than in the non-fluoridated set; the excess increase in the 65+ age-group was approximately 37 per 100,000 population (Table 4.2). The results of the other two methods of comparison used by Yiamouyiannis

and Burk were similar but not identical, although all methods were algebraically equivalent; the (F-NF) differences were lower than those given in the last column of table 4.2 below.

Table 4.2 Age-specific Cancer Death Rates for Fluoridated (F) and non-Fluoridated (NF) Cities: According to Results of Yiamouyiannis and Burk (1977, Table 6b) (see also para 4.23 below).

Age Group	Set of Cities	Average Cancer Death Rate (per 100,000)		Increase in average rate (1952-1969)	Difference of increase (F - NF)
		1952	1969		
45-64	F	337.2	377.9	40.7	16.6
	NF	324.5	348.6	24.1	
65+	F	1031.9	1072.4	40.5	36.7
	NF	974.2	978.0	3.8	

4.16 The authors claimed that the excess increases in cancer death rate in the older age-groups were statistically significant, and they concluded that the excesses were linked to fluoridation.

4.17 The data provided to Yiamouyiannis and Burk had not been sufficiently detailed to allow analysis by the more usual 5- or 10-year age-groups, or by sex or race. They anticipated objections that they might therefore have underestimated the effect of population changes, by presenting the following supplementary analyses, based on the more detailed data available for census years:

    i) **Subdivision of age-groups.** They calculated the proportion of 55-64 year olds in the 45-64 age-group, and the proportion aged 75+ in the 65+ age-group, for the census years 1950, 1960 and 1970. They reported virtually no difference, between the two sets of cities, in the changes that took place in these proportions over the period. It was implied that therefore to have used narrow age-bands would not have affected the result.

    ii) **Proportion of males.** They calculated that the proportion of males aged 45-64 and 65+, decreased faster in the fluoridated than in the non-fluoridated cities, presumably implying that, as the cancer death rate of males over 45 is generally higher than that of females over 45, correction for sex would acutally have augmented the excess increases in cancer death rates in the fluoridated cities.

    iii) **Rates in whites and non-whites.** They noted that "nationally the cancer death rate of non-whites is increasing faster than the cancer death rate of whites", and that "there is a greater increase in the percentage of non-whites in the fluoridated group of cities". However, on the basis of very briefly reported analyses, they argued that:

        a) the increase in the percentage of non-whites in the fluoridated cities occurred mainly in the two younger age-groups (in which they had detected no effect of fluoridation on cancer rates);

        b) there was no correlation between the age-standardised cancer death rate (see para 4.28 seq.) for each city, and the percentage of non-whites in the city population; nor was there a correlation between the age-specific cancer death rate for the 45-64 age-group for each city, and the percentage of non-whites in the relevant population;

c) cancer death rates did not increase more rapidly among non-whites than whites, in central cities; and that "whites and non-whites at similar degrees of urbanisation experience similar cancer death rates".

They implied that on all these grounds, adjustment for changes in the proportion of non-whites would have had no effect on the results.

Comments of the Working Party

4.18 Our comments on this study of age-specific rates are of three types. First, we comment on certain demographic aspects, that is to say, the effects of the use of broad age-bands and of the failure to standardise or otherwise incorporate adjustments for sex and race. Second, we discuss the accuracy of the data, the calculations and the method of estimation of population size. Third, we examine the trends in age-specific cancer death rates for the individual cities, and the implication of the range of individual trends for the proper interpretation of Yiamouyiannis and Burk's analyses of averages of the trends.

A. Demographic aspects

4.19 Although the analysis of age-specific rates is a step towards meeting the criticism of the use of crude rates, the division of the population into the broad age-bands used by Yiamouyiannis and Burk is inadequate. To take one example, there is commonly a three or fourfold increase in cancer death rates over the range from 45 to 64 years of age. The use of a single rate for such a range of ages is therefore likely to produce only incomplete correction of crude rates. Only 5- or at most 10-year age-groups, subdivided by sex (and, in the United States, by race) would be really satisfactory for calculating rates suitable for meaningful comparisons.

4.20 We have looked carefully at the reasons presented by Yiamouyiannis and Burk to justify their acceptance of the results based on the use of broader age-groups without subdivisions by sex or race, and the calculations presented in their paper have been checked.

i) **Subdivision of age-groups.** The authors' presentation of the age-distribution within the two older age-groups in census years contains some inaccuracies. Recalculation shows that both the proportion of 55-64 year olds in the 45-64 age-group, and the proportion aged 75+ in the 65+ age-group, increased slightly more from 1950 to 1970 in the fluoridated cities than in the non-fluoridated cities.

ii) **Proportion of males.** Our calculations confirmed that the proportion of males aged 45-64 years decreased slightly more in the fluoridated cities. They also showed that the proportion of males aged 65 or more increased slightly more in the fluoridated cities.

iii) **Rates in whites and non-whites.** The increase in the percentage of non-whites, from 1950 to 1970, was greater in the fluoridated cities for all four broad age-groups. Contrary to the conclusions of Yiamouyiannis and Burk, there is a great deal of evidence that non-whites experienced different cancer death rates from whites, in the cities and years covered by this study (e.g. see Appendix Table B of Kinlen and Doll, 1981). This is sufficient to indicate that adjustment for race might have an important effect on the results.

4.21 Although consideration of the demographic aspects one at a time may appear to suggest that further adjustment of the age-specific rates in terms of race alone would be satisfactory, this is a false conclusion. Cancer death rates are strongly related to age, and small alterations of the age-distribution of a

47

population can produce large alterations in the average cancer death rate. Further, the difference between cancer death rates for whites and non-whites shows a complicated dependence on age and sex (Fig. 2). Simultaneous standardisation for age (in 5- or 10-year bands), race and sex is therefore required, and the arguments of Yiamouyiannis and Burk do not eliminate the necessity.

4.22 Taves (1979) has evaluated the effect of using Yiamouyiannis and Burk's broad age-bands and disregarding sex and race. He found that half of the excess increase in the average cancer death rate of the 45-64 year age-group in the fluoridated cities could be explained on the basis of the changes in age, race and sex composition. None of the excess increase for the 65 + age group could be explained in this way, but Taves indicated that he had found errors in the data and analyses of Yiamouyiannis and Burk, and he suggested that other errors may be contributing to the apparent residual increases in the older age-groups.

B. Accuracy of Data and Calculations

4.23 In checking the data and analyses reported by Yiamouyiannis and Burk (1977), we ourselves have discovered many errors. One example is the use of the wrong figure for the number of years (18 instead of 17) in some of the calculations. Another is the failure of the algebraically equivalent procedures used in the computation of the trend-lines (see para 4.14) to yield identical results. One of the errors in the data had an important effect on the results. In the worksheets available to the Working Party, the population for the 45-64 age-group in Pittsburgh in 1970 was given as 105,964. Ths is actually the size of that group in Buffalo; the correct figure for Pittsburgh should be 129,230. The population estimates back to 1961 are affected. The rates calculated on that erroneous basis are included in the authors' paper. Recalculation, correcting this and other smaller errors, reduces the apparent excess increase in the cancer death rate of the 45-64 age-group in the fluoridated cities by about half. The effect of this error, together with the independent effect of the changes in age, race and sex composition explored by Taves, could therefore account for the whole of the excess increase in cancer death rate claimed for this age-group by Yiamouyiannis and Burk. The results for the 65 + age-group are not affected by the error in the Pittsburgh data.

4.24 A rather different question of accuracy concerns the method of estimation of population size used by Yiamouyiannis and Burk. They have argued that their analyses were superior in that they used data on cancer deaths for the years between censuses. To calculate death rates for those years, however, intercensal population numbers must be used, and these are not usually available. To overcome this difficulty, throughout the four types of analysis described in this chapter, Yiamouyiannis and Burk estimated intercensal populations by the method of linear interpolation. This is a widely used technique which represents a commonsense approximation; it does, however, introduce an uncertain degree of error. An example of the possible error may be seen in the calculation of the intercensal population for Washington DC (one of the fluoridated cities), whose population has been estimated officially for each year (because it is coterminous with the District of Columbia). Between 1940 and 1970, the officially estimated population of Washington DC frequently differed considerably from the linear interpolation estimate (Fig. 3). The first decade (1940-1950) is likely to be atypical because it includes the war years, but the difference is still marked in the second and third decades. The effect of the erroneous population estimates on the apparent death rates can be large; thus, recalculation of the crude cancer mortality rates (all ages combined) for this city, using the

official annual population figures, shows that the upward trend in crude cancer mortality measured in this way began in 1944 (that is, before fluoridation), rather than in the post-fluoridation year of 1955 as would be suggested by inspection of the linear interpolation estimate (Chilvers, 1983).

Figure 3 Intercensal population estimates for Washington DC
(Chilvers, 1983)
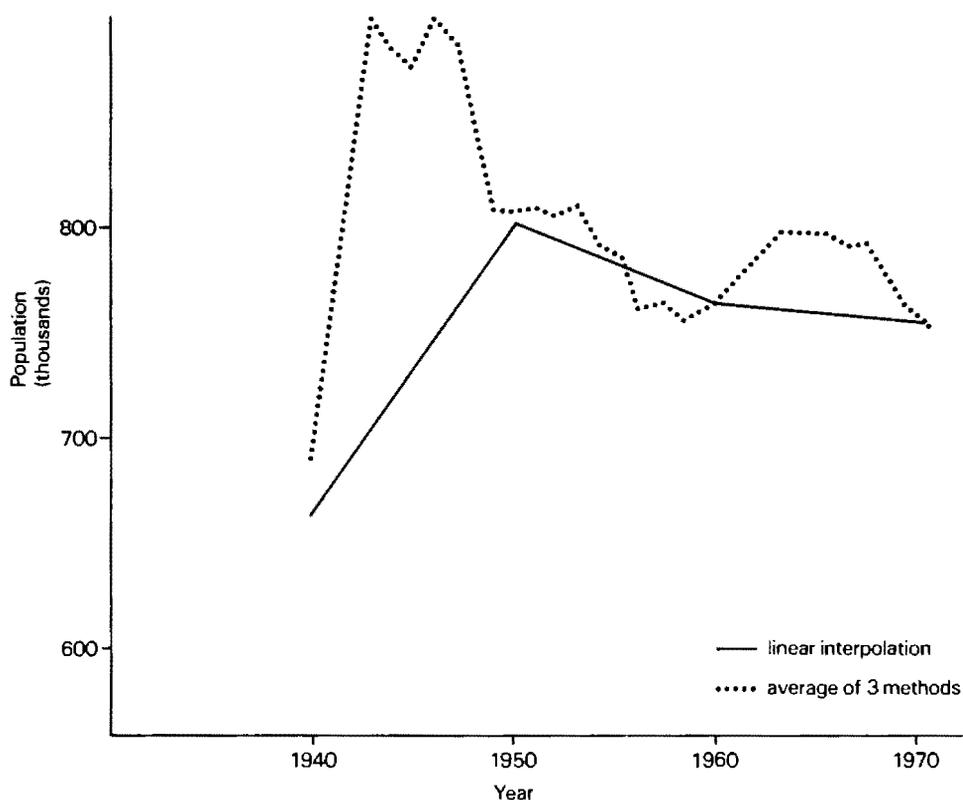
C. Trends in Individual Cities

4.25 We have seen that Yiamouyiannis and Burk claimed that the age-specific cancer death rates, in the 45-64 age-group and in the 65 + age-group, rose more in the fluoridated cities than in the non-fluoridated cities. We have noted that the apparent excess increase in the 45-64 age-group can be attributed partly to demographic changes and partly to errors in the data, but that the excess increase in the 65 + age-group cannot be explained in this way. In order to interpret these differences between the average trends in cancer death rates for the two sets of cities, it is essential to examine the trends in the twenty individual cities. This has been done by Maritz and Jarrett (1983) using the data given by Yiamouyiannis and Burk. The results for the 65 + age-group are presented in Figure 4. It is clear that there was a wide range of trends, and moreover that the range of trends in the ten fluoridated cities was similar to that of the ten non-fluoridated cities. This conclusion applies to each of the four age-groups.

Figure 4 Crude Cancer death rates in individual cities: changes 1952 — 1969
(Data from Maritz and Jarrett, 1983)
Results for the 65+ years age group
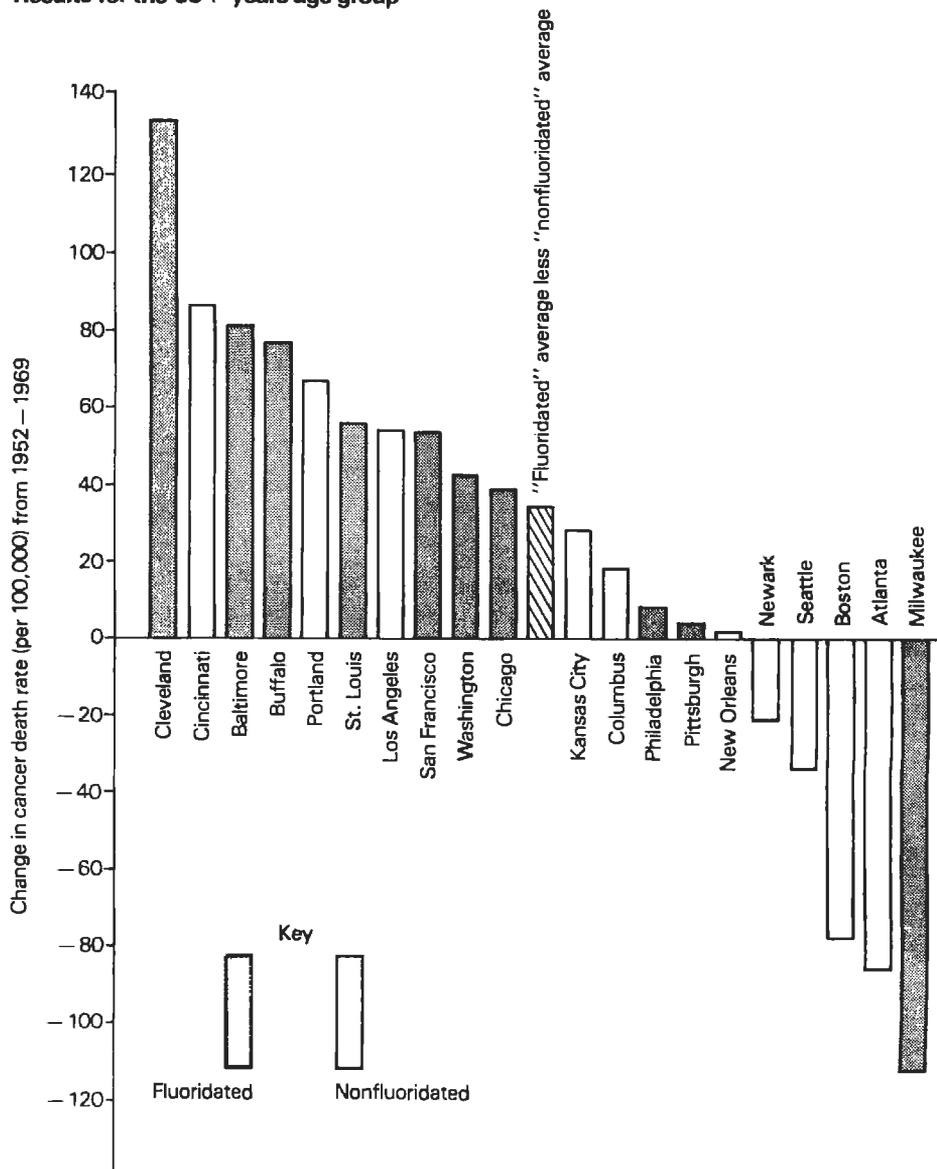
4.26 In their calculation of the statistical significance of the excess increases which they claimed, Yiamouyiannis and Burk failed to take account of the inconsistencies in the trends between different cities in the same set. The correct way to examine the trends has been demonstrated by Maritz and Jarrett (1983); the outcome is that the difference in trends between the two sets of cities, for the 65+ age-group, could have arisen by chance with a probability as large as 1 in 4. Put another way, if ten cities were picked at random from the whole group of 20, and compared with the other ten, then one out of every four such possible comparisons would yield a difference at least as large as that found by Yiamouyiannis and Burk. A similar conclusion applied to the difference reported for the 45-64 age-group, even without taking account of the errors in the reported figures (see paragraphs 4.22 and 4.23).

4.27 Correct calculation of statistical significance therefore shows that the differences found by Yiamouyiannis and Burk between the average age-specific trends are not at all surprising. Such differences would be expected to occur quite commonly because of the wide range of the trends in age-specific cancer death rates for the individual cities. The analysis of the age-specific rates provides no sound evidence for a link between fluoridation and cancer.

CANCER DEATH RATES DIRECTLY STANDARDISED FOR AGE

Data and Calculations

4.28 Where death rates are available for subgroups of a population, 'direct standardisation' provides a single summary figure which reflects the overall pattern of results and allows comparisons, between places or times, which are not distorted by differences in the demographic compositions of the populations concerned. (A fuller explanation is given in Appendix 1). When making such comparisons, it is necessary to base them on the demographic composition of a single 'reference' population (the 'standard' population).

4.29 Yiamouyiannis and Burk (1977) use direct standardisation as a method of combining the results of the separate age-groups described in the preceding section of this report. Full details of their method of calculation were not set out in the paper, but they appear to have been as follows:

  i) Two reference populations — one for 1952 and one for 1969 — were constructed from the combined populations of the twenty cities. (The text of the paper appears to state that a single reference population was used, intermediate between 1952 and 1969, but that interpretation is incorrect).

  ii) The age-specific cancer mortality rate for the 0-24 age-group (for example) in the fluoridated cities in 1952 had already been estimated as explained in paragraph 4.14. This was multiplied by the estimated number of people in that age-group in the 1952 reference population to produce a hypothetical 'number of deaths'. The same procedure was applied to each age-group in the fluoridated set and then in the non-fluoridated set; and also for 1969, but using the 1969 reference population.

  iii) The four 'numbers of deaths' for the fluoridated set of cities in 1952 were added, the result being divided by the estimated size of the 1952 reference population. The same procedure was applied to the non-fluoridated set, and to each set for 1969 using the 1969 reference population. The resulting four numbers were the 'directly age-standardised cancer death rates'.

Presentation and Interpretation

4.30 The three methods of calculation of the age-specific death rates had produced three different sets of results (see para 4.15), and therefore the authors also presented three different sets of results based on age-standardised rates. The results for one of the three versions of this analysis are given in Table 4.3 below.

Table 4.3 Directly Age-Standardised Cancer Death Rates (per 100,000) for Fluoridated (F) and non-Fluoridated (NF) Cities: Yiamouyiannis and Burk, 1977.

Set of Cities	Average Age-Standardised Rate		Increase in Average Rate (1952 to 1969)	Difference of increases (F — NF)
	1952	1969		
F	188.25	217.46	29.21	7.78
NF	178.83	200.26	21.43	

4.31 The differences (F - NF) in the other two analyses were 8.64 and 9.20. The authors concluded that ''the age-corrected cancer death rates .... reflect 8-9 more cancer deaths per 100,000 population per year in the fluoridated cities than in the non-fluoridated cities''. They implied, although they did not state, that this excess was due to fluoridation.

Comments of the Working Party

4.32 This analysis is built on to the age-speciifc analysis considered earlier, and carries through most of the flaws of that analysis. In particular, the criticisms that the age-bands are too broad, and that no adjustments are made for race and sex, are still pertinent; the effect of the erroneous value for the number of people aged 45-64 years in Pittsburgh in 1970 remains; and the calculations still rely on intercensal population estimates obtained by linear interpolation.

4.33 In standardisation procedures only a single reference population should be used for each set of comparisons (see 'The Choice of Standard Population' in Appendix 1). Yiamouyiannis and Burk, however, constructed separate reference populations for 1952 and 1969. Although it is valid to use these figures for comparisons of the fluoridated and non-fluoridated cities at each point in time, it is invalid to use this method in order to compare mortality in 1952 with that in 1969. Although, in this instance, recalculation using a single, intermediate, reference population does not alter the results greatly, it does indicate that the use of the two reference populations has somewhat magnified the already spurious difference between the rates in the fluoridated and non-fluoridated sets of cities. It should also be noted that Yiamouyiannis himself subsequently condemned the use of multiple reference populations in the work of others (Yiamouyiannis 1979).

4.34 The directly age-standardised rates therefore provide results which are certainly no more reliable, and probably less reliable, than the inaccurate age-specific rates on which they are based. We note also that Yiamouyiannis and Burk failed to present calculations of the statistical significance of their results.

CANCER DEATH RATES INDIRECTLY STANDARDISED FOR AGE, RACE AND SEX

Data and Calculations

4.35 Indirect standardisation is an alternative to direct standardisation, and is a commonly used method of allowing for demographic differences in populations (see Appendix 1). It can be used when all that is known about the deaths from a particular disease in each population is the total number. Results obtained using indirect standardisation are usually similar to those using direct standardisation. Indirect standardisation, rather than direct standardisation, for age, sex and race, has been used by several authors who have reanalysed the 20-city data (see Chapter 5), for the following reasons:

a) direct standardisation for age, sex and race is not possible unless the numbers of deaths in the appropriate subgroups are available. Only the total numbers of cancer deaths (not subdivided by age, sex or race) are published in generally accessible form for many of the cities and years in question.

b) the data obtained from individual cities by Yiamouyiannis and Burk and which were used in their direct standardisation for age (discussed in the previous section), were not generally adequately subdivided by sex or race or age-groups.

4.36 Yiamouyiannis and Burk (1977) have criticised indirect standardisation as a method, but, following its use by others on the 20-city

data*, Yiamouyiannis presented four different analyses of the official data, using his own variants of the method of indirect standardisation, and reaching conclusions different from those of the previous authors. One analysis was reported in a letter to the Lancet (Yiamouyiannis, 1978), the others in the course of legal proceedings (Winner et al., 1978) or Congressional hearings (Yiamouyiannis, 1977). Several of the details of the methods used by Yiamouyiannis became available only when they were sent with the results of the fourth analysis supplied, by request, to the Department of Health and Social Security (Yiamouyiannis, 1980). In order to understand this fourth analysis, it is necessary to follow each step as the author performed it:

a) **Calculation of 'observed cancer death rate'.**

(Steps (i) to (iv) are almost identical to the calculation of crude rates outlined in para 4.6).

(i) The total number of deaths from cancer of all sites together (for men, women, all ages and all races combined), for each city separately, and for each of the years 1950 and 1953-68, was obtained from successive volumes of 'Vital Statistics of the United States'.

(ii) The population of each city was obtained from the official census reports of 1950, 1960 and 1970. The size of the populations for each of the intermediate years was estimated by linear interpolation.

(iii) Crude cancer death rates were then calculated for each city for each of the years 1950 and 1953-68, by dividing the number of deaths by the total enumerated (or estimated) population.

(iv) For each year, the calculated crude rates for the ten fluoridated cities were added together, and then divided by the number of those cities; the procedure was repeated for the non-fluoridated cities. The result was two series of unweighted averages of the crude annual rates, one series for the set of fluoridated cities, and one series for the set of non-fluoridated cities.

(v) For each set of ten cities, the trend in the average crude cancer death rate was calculated by the technique of linear regression. From the trend-line, an <u>estimated</u> average crude death rate was read off for 1950; the line was also extended to allow an <u>estimated</u> average crude death rate for 1970 to be read off (linear extrapolation). Each of those figures was called the 'observed death rate' for the appropriate year, for that set of cities.

b) **Calculation of 'expected cancer death rate'.**

In contrast to the method used to obtain the 'observed death rate', the 'expected death rate' was calculated from data for census years only, as follows:

(vi) For each city, the population numbers, classified into 5-year age-groups, for males and females separately, and whites and non-whites separately, were used to calculate the 'expected' number of deaths from cancer in 1950 and 1970. The set of standard rates used in this calculation was the set of observed rates for the population of Washington DC in 1960.

(vii) For each city, the total number of 'expected' deaths for 1950 or 1970 was divided by the total population of that city in the appropriate year (that is, the numbers were converted to rates).

(viii) For each year (1950 or 1970), these rates for the ten fluoridated cities were added, and then divided by the number of these cities; the procedure was repeated for the non-fluoridated cities. The resulting unweighted averages were called the 'expected death rates'.

c) **Calculation of the 'Standardised Mortality Ratio'**

(ix) For each year (1950 or 1970) and for each set of ten cities (fluoridated or non-fluoridated) the 'observed death rate' from (v) was divided by the 'expected death rate' from (viii). The result was the 'Standardised Mortality Ratio (SMR)' as defined by Yiamouyiannis, and this was the figure which was used for subsequent comparisons.

Presentation and Interpretation

4.37 The results of all four of Yiamouyiannis's analyses by this form of indirect standardisation are given in Table 4.4. Yiamouyiannis variously concluded that there was an excess increase of some 3% (Yiamouyiannis, 1977) to 6% (Winner *et al.*, 1978) in the 'Standardised Mortality Ratio' in the fluoridated cities.

Table 4.4 Standardised mortality ratios for fluoridated (F) and non-fluoridated (NF) cities: Yiamouyiannis's four indirect standardisations.

Reference	Standard Rates (step vi)	Average of Crude death rates (steps iv and viii)	Sets of cities	Average SMR		Increases in average SMR (1950-to 1970)	Difference of increase F — NF
				1950	1970		
1. Yiamouyiannis 1977; Winner *et al*, 1978	US 1950	Weighted	F	1.261	1.271	0.010	0.042
			NF	1.174	1.142	−0.032*	
2. Yiamouyiannis 1978	Not stated	Unweighted	F	1.023	1.111	0.088	0.045
			NF	0.961	1.004	0.043	
3. Winner *et al*, 1978	Washington 1960	Unweighted	F	1.08	1.13	0.05	0.06
			NF	1.03	1.02	−0.01	
4. Yiamouyiannis 1980	Washington 1960	Unweighted	F	1.078	1.108	0.03	0.047
			NF	1.042	1.025	−0.017	

*Calculated by us from the figures for 1950 and 1970; the figure quoted in the paper was −0.028.

4.38 The conclusions from another series of indirect standardisations, including SMRs estimated for 1940, have been circulated by Burk and Graham (Burk and Graham, 1984; Graham and Burk, 1984). It appears that the SMRs were calculated in the manner described above; in particular, the only available detailed results apparently stem from an analysis identical to Yiamouyiannis's first indirect standardisation, although the SMRs calculated by Burk and Graham differ somewhat from those obtained by Yiamouyiannis.

Comments of the Working Party

4.39 The comments below are directed principally to the fourth indirect standardisation (Yiamouyiannis, 1980), as it is the only one for which adequate detail has been provided. The reason for the differences between the results of the third analysis, as put to a court of law in Pennsylvania (Winner *et al.*, 1978), and the fourth analysis, as explained in detail (Yiamouyiannis, 1980), is not known to the Working Party; on the face of it, the methods used were the same. It would seem, however, that the major comments apply to all the analyses.

4.40 Our comments are of two types. First, we examine several technical details which have been emphasized by Yiamouyiannis. Second, we consider the trends in SMRs for the individual cities, and the implication of the range of trends for the proper interpretation of Yiamouyiannis's results.

A. Technical Details

4.41 Yiamouyiannis (1977, 1978, 1979) has emphasised that his method of indirect standardisation was unlike that adopted by all other authors, in three respects in particular:

(i) he did not use the erroneous figure for the number of cancer deaths in 1970 in the non-fluoridated cities which had been used in the earlier indirect standardisations by the National Cancer Institute (Frederickson, 1976) and others (Doll and Kinlen, 1977; Oldham and Newell, 1977). These studies and the corrected results as later published by the authors, are discussed in Chapter 5;

ii) he did not restrict his analysis to census years, but included data on cancer deaths for intercensal years;

iii) he excluded data for 1970, when fluoridation had commenced in certain of the non-fluoridated cities.

The first of these points is addressed in the following chapter (Chapter 5), where it will be seen that correction of the data did not affect the conclusion reached by the other authors, namely that there was no effect of fluoridation on cancer mortality. The second and third points are discussed below. It should be noted that these matters principally affect the calculation of the 'observed cancer death rates' for 1950 and 1970 (see para 4.36(a)).

4.42 As in all the analyses discussed in this chapter, Yiamouyiannis's use of data on cancer deaths for intercensal years required that he estimated the intercensal population numbers (step (ii) of his calculations), thus introducing an uncertain degree of error (see para 4.24). It would be safer to avoid this source of possible error by adopting the normal practice of centering the calculation of the standardised mortality rations (SMRs) on, or closely around, the census years, thus using population estimates which would be expected to be more reliable.

4.43 Yiamouyiannis however, had argued (Winner et al., 1978) that the official figures for numbers of deaths from cancer in 1970 could not be used to calculate the observed cancer death rate, because two cities in the non-fluoridated set had fluoridated by that time (Atlanta and Seattle fluoridated in 1969). It is, however, most unlikely that such a brief period of fluoridation could substantially affect the results even if the hypothesis that fluoridation causes cancer almost immediately were to be accepted: only a few types of cancer are so rapidly fatal. The point has been examined directly, and it is clear that the exclusion of these two cities has no important effect on the results (Kinlen and Doll, 1981; Chilvers, 1983; see Chapter 5). Yiamouyiannis was inconsistent in that, despite his objections to the use of Atlanta and Seattle, he continued to include Kansas City, which fluoridated for two years from 1962 to 1964, in the set of non-fluoridated cities.

4.44 Yiamouyiannis's wish to use the number of cancer deaths for each year and, perhaps, his objection to the use of 1970 figures, led him to construct a trendline through his estimated year-by-year cancer death rates and to use this to further estimate the 'observed' cancer death rates for 1950 and 1970 (step (v) of his calculation). It is a simple matter to calculate the actual observed cancer death rates for these census years, from official data, and this is the normal practice. The results from the two methods are given for comparison in Tables 4.5 and 4.6

Table 4.5 Estimated 'Observed' Crude Cancer Death Rates (per 100,000) for Fluoridated (F) and non-Fluoridated (NF) cities: Yiamouyiannis, 1980.

Set of Cities	'Observed' Average Cancer Death Rate		Increase in Average Rate (1950 to 1970)	Difference of increase (F — NF)
	1950	1970		
F	184.5	230.5	46.0	
NF	182.9	198.0	15.1	30.9

Table 4.6 'Observed' Crude Cancer Death Rates (per 100,000) for Fluoridated (F) and non-Fluoridated (NF) Cities: Equally-Weighted Averages. (Calculation for the Working Party)

Set of Cities	'Observed' Average Cancer Death Rate		Increase in Average Rate (1950 to 1970)	Difference of increase (F — NF)
	1950	1970		
F	179.5	224.7	45.2	
NF	179.0	203.4	24.4	20.8

4.45 It is clear that Yiamouyiannis's method resulted in a considerable overestimate of the difference between the two sets of cities in 1970, to the disadvantage of the fluoridated set. This in turn inflated the difference between the two sets with respect to the changes in the SMRs from 1950 to 1970. Yiamouyiannis's method accounted for most of the difference which he reported between the trends for the two groups of cities.

4.46 Yiamouyiannis (Winner *et al.*, 1978) claimed that his later indirect standardisations were preferable in two further respects. The first of these is his use of the rates of Washington, D.C. as the standard rates (where other authors had used the rates of the United States population). While the use of standard rates from a reference population close in character to the study population is desirable, so too are standard rates from a population of substantial size. It is unlikely in this case that the choice of reference population has greatly affected the result; that the use of any of a variety of suitable populations does not do so has been shown directly (see Chapter 5).

4.47 Yiamouyiannis's second claim refers to his use of equally weighted (unweighted) averages in the calculation of 'observed' and 'expected' death rates (steps (iv) and (viii) of his calculations), a procedure which he and Burk adopted for almost all analyses considered in this chapter. The consequence of equal weighting of the crude death rates is that each city is treated as an equally important unit, irrespective of the size of its population; this also means, however, that an individual in a large city has less statistical importance than one in a smaller city. The usual alternative method, of weighting by population size, gives individuals identical importance. There are reasonable arguments for both techniques, but it would not be expected that the final results of the present analyses would be greatly affected, as the range of population sizes is not very large; that this is so has been confirmed in calculations performed for the Working Party.

4.48 We have seen that none of the five points which Yiamouyiannis has emphasised in his method of indirect standardisation provides a reason to prefer his approach to more conventional methods. On the contrary, his procedure for calculation of the 'observed' cancer death rate by interpolation and extrapolation is open to question, and his arguments for adopting this procedure are unconvincing.

B. Trends in Individual Cities

4.49 Even if there were no doubt about the validity of Yiamouyiannis's SMRs, it would still be necessary to examine whether the difference between the trends of the average SMRs in the two sets of cities could have arisen by chance. Nowhere in his available analyses did Yiamouyiannis attempt to do this. In order to do so adequately, it is essential, as with the age-specific rates (paras 4.25 to 4.27), to consider the trends for the individual cities. It is not possible to do this within the framework of computation that Yiamouyiannis adopted, but an assessment undertaken for the Working Party (Chilvers, 1983) has demonstrated that, as with the age-specific rates, the twenty cities showed a wide range of trends in SMR, and that the range for the ten fluoridated cities was similar to that for the ten non-fluoridated cities. A difference between the average SMRs of at least the magnitude claimed by Yiamouyiannis could easily arise if fluoridation had no effect and the twenty cities were to be split randomly into two sets of ten (Figure 5). This being so, even if a difference of the order reported by Yiamouyiannis had been calculated by sound methods, it would have been invalid to conclude that it was attributable to anything but chance.

Figure 5 Standardised mortality ratios in individual cities: changes 1950–1970
(Data from Chilvers, 1983)

57
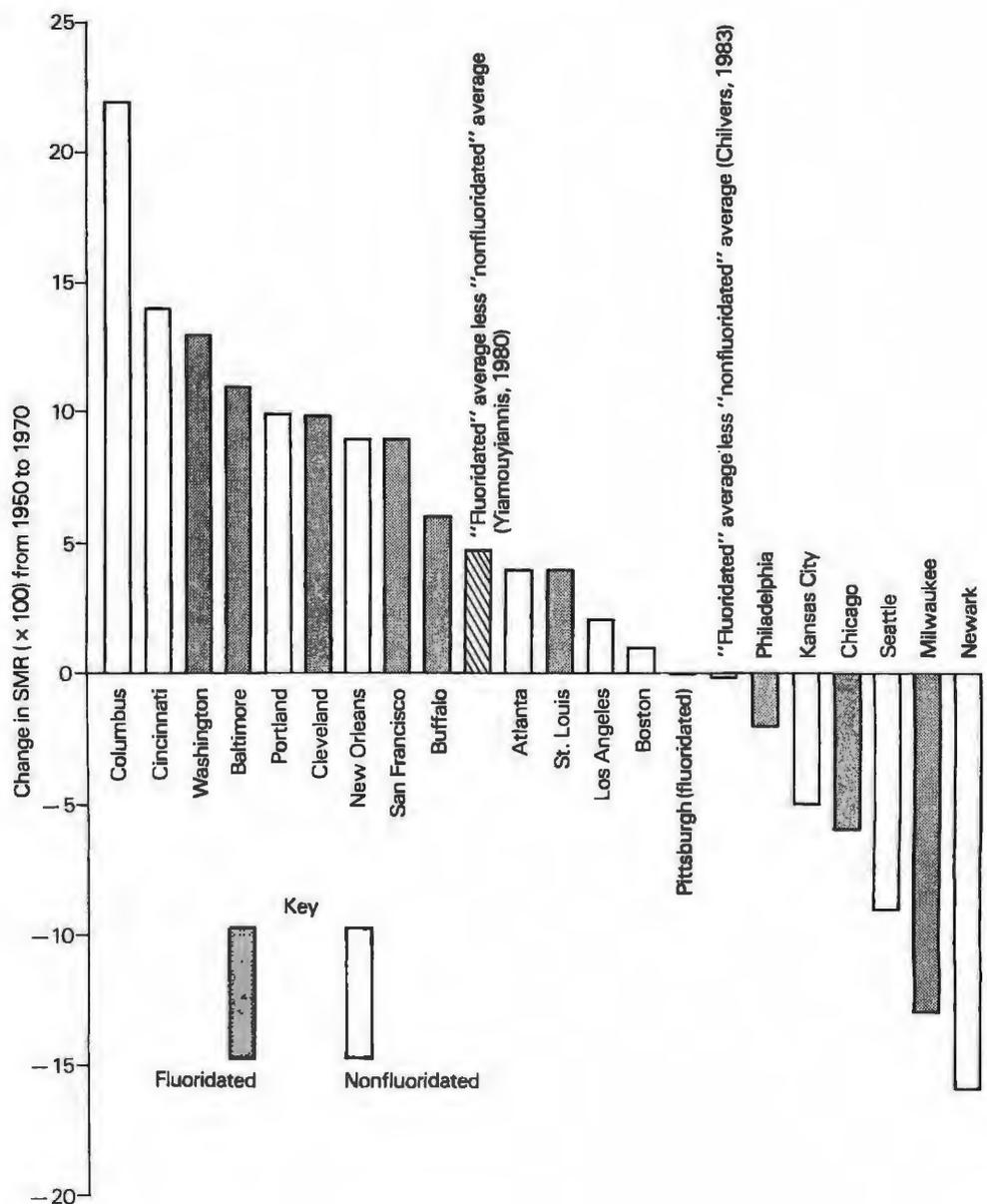
**DISCUSSION OF
STUDIES
CONSIDERED IN
CHAPTER FOUR**

4.50 This chapter has devoted much attention to technical issues: at times, it must have seemed, almost to the point of pedantry. This was inevitable. Yiamouyiannis and Burk have repeatedly focused attention on details, and it was therefore necessary to examine their studies at that level. Our major points of criticism, however, all rest on the general scientific principles indicated in Chapter 1. There are three main types of defect, crucial to interpretation, in these analyses by Yiamouyiannis and Burk. They underlie and undermine thier results and their conclusions. They can be summarised as follows.

4.51 The first major weakness is the failure to make the comparisons between cancer death rates in different populations as fair as possible with regard to the demographic structure of the populations that are being compared. Different patterns of migration have caused the proportions of the population, of various ages, white or non-white, male or female, to alter in different ways in the fluoridated and non-fluoridated cities, with profound effects on crude cancer death rates. Only the indirect standardisations have allowed fully for the demographic changes, although in an unorthodox and questionable fashion.

4.52 The second group of defects includes the many mistakes or inconsistencies in the authors' handling of their data. One important example was the error in the Pittsburgh population, which distorted one of the age-specific rates. In general, the impression gained from the original presentations has been one of confusion and needless complication. Apparently equivalent algebraic procedures in the comparison of age-specific trends yielded three different answers, and the choices of computational and statistical methods were inappropriate and inept. The reasons given by the authors for their departures from standard practice, in an area such as indirect standardisation where satisfactory techniques already exist, are unconvincing.

4.53 Even if the methods had been correct and the results reliable, it would still have been necessary for the authors to demonstrate that the claimed effect of fluoridation was 'significant', in the sense of being distinguishable from the background changes in cancer mortality rates. Unless this were so, no firm conclusion could be based on their results, and any biological interpretation would be pure speculation. The failure of Yiamouyiannis and Burk to conduct acceptable statistical tests, and the absence of statistical significance when such tests of their results have been performed by others, constitute the third defect in the time trend studies, and in the conclusions which Yiamouyiannis and Burk drew from their results.

4.54 There is a further and fundamental reservation about these studies. Their preoccupation with the combination of all cancers and with the search for an effect following swifly on fluoridation is difficult to justify in the light of existing biological knowledge. Studies directed at hypotheses which accord better with our understanding of the manner by which chemicals may cause cancer will be reviewed later in the report, and the issue will be discussed in Chapter 9. In the first instance, however, we shall look at other studies analysing cancer mortality in the twenty cities considered by Yiamouyiannis and Burk.

CONCLUSION TO CHAPTER FOUR

4.55 The United States time-trend studies by Yiamouyiannis and Burk are so seriously flawed that their conclusion of a 'linkage' between increases in cancer mortality and the introduction of fluoridation is untenable. For more valid analyses it is necssary to look to studies of the same general type that have been undertaken by other workers.

CHAPTER 5

STUDIES OF THE "20 UNITED STATES CITIES" BY OTHER AUTHORS

INTRODUCTION

5.1 Several investigators have re-analysed cancer mortality in the set of 20 cities chosen by Yiamouyiannis and Burk (1977), or in modifications or extensions of that set. None found any effect on cancer mortality attributable to fluoridation. A number of these papers also explored the demographic characteristics of the 20 cities, and the effects that changes in those characteristics were bound to have on cancer mortality rates (e.g. Doll and Kinlen, 1977; Oldham and Newell, 1977). Others studied the effects, on results, of the particular variants of the method of indirect standardisation advocated by Yiamouyiannis, and demonstrated the very different conclusions which result from appropriate, well-validated and correctly performed methods of analysis (e.g. Kinlen and Doll, 1981; Chilvers, 1983).

THE UNITED STATES NATIONAL CANCER INSTITUTE STUDY

5.2 The United States National Cancer Institute (Frederickson, 1976) employed the method of indirect standardisation (see Appendix 1) in its calculations. The 'expected' number of cancer deaths in each of the two groups of cities, fluoridated (F) and non-fluoridated (NF), for the relevant census years, was calculated by multiplying the age and sex-specific cancer mortality rates for whites and non-whites in the 1950 U.S. population by the reported population totals in the appropriate categories in each group of cities. The mortality rates used were those for 5-year age-groups. The standardised mortality ratio (SMR) for each of the two groups of cities in each census year was calculated by dividing the actual (observed) number of deaths by the 'expected' number. The SMRs for 1950 (just preceding the commencement of fluoridation in these cities) and for 1970 are shown in Table 5.1

Table 5.1 Standardised mortality ratios for the 20 cities (data from Frederickson, 1976).

	(1)	(2)	(3)	(4)	(5)	(6)
Set of cities	Average SMR		Increase in average SMR (1950 to 1970) (b-a)	Difference of increase F — NF	% Increase $\frac{b-a}{a} \times 100$	Difference of % increase F — NF
	1950 (a)	1970 (b)				
F	1.23	1.24	0.01	−0.03	1	−2
NF	1.15	1.19	0.04		3	

5.3 The percentage increase was very similar in the two groups (column 5), although it was slightly greater (by 2 %) in the non-fluoridated cities (column 6). There were, however, errors in the data; most were minor, but two of them affected the results. The size of the non-fluoridated non-white female population aged 65-74 in 1970 was overestimated, and in transcription the whole of Suffolk county had been included inadvertently with Boston city, resulting in too large a figure for the 1970 cancer deaths in the non-fluoridated cities. The effect of these errors was an incorrectly high average SMR for the non-fluoridated cities in 1970. After correction (Hoover, 1977), the small percentage increases for the two groups were almost identical (Table 5.2).

Table 5.2 Standardised mortality ratios for the 20 cities (data from Hoover, 1977).

	(1)	(2)	(3)	(4)	(5)	(6)
Set of cities	Average SMR		Increase in average SMR (1950 to 1970) (b-a)	Difference of increase F — NF	% Increase $\frac{b-a}{a} \times 100$	Difference of % increase F — NF
	1950 (a)	1970 (b)				
F	1.23	1.24	0.01	−0.01	1	−1
NF	1.15	1.17	0.02		2	

THE ROYAL STATISTICAL SOCIETY STUDY

5.4 A more detailed statistical examination of the National Cancer Institute data was commissioned by the Royal Statistical Society in response to an approach by the Royal College of Physicians. The authors (Oldham and Newell, 1977) noted the complicated dependence of cancer mortality on age, sex and race, and in particular the considerable differences between cancer mortality in the age-groups 65-74, 75-84 and 85 +, and between the sexes and races within these groups (see figure 2 above). In describing the use of broad age-groups by Yiamouyiannis and Burk, Oldham and Newell pointed out that "this means that any analysis which puts together either all the over-65s regardless of race, or all the non-whites regardless of age, will obscure rather than clarify any real differences".

5.5 Turning to population structures, Oldham and Newell noted that the two groups of cities differed in 1950. The cities which were to be fluoridated started with many fewer elderly white females, fewer elderly white males, and more non-whites at all ages below 55. Despite these differences, the cities which were to be fluoridated already had, in 1950, an excess of cancer deaths which was not only over and above that to be expected on the basis of the population structure, but which was also 10.3 per 100,000 population greater than the excess in the non-fluoridated cities.

5.6 The demographic differences were even greater by 1970. The fluoridated cities had many more non-whites of all ages, and many fewer whites under the age of 55. They were therefore much more likely to have deaths from cancer.

5.7 Having demonstrated that it was essential to allow for demographic changes, Oldham and Newell analysed the data by the same method as the National Cancer Institute, and obtained the same results (though expressed in a slightly different form). The data contained the same errors as noted previously; Oldham and Newell (1979) subsequently recalculated from the corrected data, their results then agreeing with the corrected results of the National Cancer Institute (Hoover, 1977).

5.8 The results from the corrected data did not alter their conclusion that when demographic changes were taken into account, there was very little difference between the changes in cancer mortality in the two groups of cities. They found "no scope for a major role for fluoridation as a cause of cancer mortality".

DOLL AND KINLEN, 1977

5.9 These authors noted, as had Oldham and Newell, that the proportion of non-whites, and the proportion of the population aged over 65, had increased more in the fluoridated than the non-fluoridated cities, and they indicated the necessity for full standardisation of cancer rates. They calculated SMRs for 1950, 1960 and 1970 from the original data of the National Cancer Institute, but their reference rates for each census year were those of the United States

population for each corresponding year (that is, a year-specific standard). The SMRs for 1960 and 1970 were therefore different from those in the studies by the National Cancer Institute and Oldham and Newell, which had used the 1950 United States population for the reference rates throughout the calculations. Doll and Kinlen's results for 1950 and 1970 are shown in Table 5.3.

Table 5.3 Standardised mortality ratios for the 20 cities (data from Doll and Kinlen, 1977).

Set of cities	Average SMR	
	1950	1970
F	1.23	1.18
NF	1.15	1.17

5.10 Correction of the errors in the data (Kinlen and Doll, 1977) altered the 1970 SMR in the non-fluoridated cities from 1.17 to 1.15. The conclusion was unaltered — namely, that there was no reason to suppose that fluoridation was associated with an increase in cancer mortality. The basis for the analysis, however, is open to criticism because more than one set of reference rates was used in the temporal comparison (see paras 4.33 and 5.17).

5.11 Smith (1980) conducted a very similar analysis (based on data taken from the 1977 paper of Doll and Kinlen) which agreed with the above results. He concluded that "a human population study which has been used to suggest that fluoridation causes cancer in fact provides additional evidence of the safety of fluoridation when the data from the study cities are analysed as appropriately as is possible."

TAVES, 1979

5.12 Taves explored the SMRs in several ways. His data for the 20 cities were obtained independently from the published source. His method also differed from that of the previous authors in that, in calculating the 'observed' number of deaths, he used the average of the observed cancer deaths for the census year and the preceding year. This use of pericensal years is a recognised technique, the aim being to gain more precision by smoothing out some of the temporal variation in annual death rates.

5.13 It had been argued by Yiamouyiannis (Winner et al., 1978) that the use of reference rates from the total United States population may not have been appropriate. For this reason, Taves also examined the effect of using the rates derived from those 15 of the 20 original cities (or the corresponding counties) for which suitable data were by then available.

5.14 The results are shown in Table 5.4. The differences between the trends for the sets of fluoridated and non-fluoridated cities were very small, and not statistically significant.

5.15 Taves proceeded to show that two further groups of cities (the ten next largest fluoridated cities, and the five non-fluoridated cities excluded by Yiamouyiannis and Burk in their selection) also exhibited similar trends in SMRs. He repeated the above analyses for the expanded set of 35 cities (Table 5.5).

Table 5.4 Standardised mortality ratios for the 20 cities (data from Taves, 1979). (Small discrepancies within this table result from the rounding of numbers).

Reference Rates	Set of cities	Average SMR		Increase in average SMR (1950 to 1970) (b-a)	Difference of increase F — NF	% Increase $\underline{b\text{-}a}$ x 100 a	Difference of % increase F — NF
		1950 (a)	1970 (b)				
U.S. 1950	F	1.2302	1.2529	0.0227	0.0067	1.8	0.4
	NF	1.1498	1.1659	0.0160		1.4	
15 cities	F	1.0120	1.0301	0.0181	0.0018	1.8	0.1
	NF	0.9539	0.9702	0.0163		1.7	

Table 5.5 Standardised mortality ratios for 35 cities (data from Taves, 1979). (Small discrepancies within this table result from the rounding of numbers).

Reference Rates	Set of cities	Average SMR		Increase in average SMR (1950 to 1970) (b-a)	Difference of increase F — NF	% Increase $\underline{b\text{-}a}$ x 100 a	Difference of % increase F — NF
		1950 (a)	1970 (b)				
U.S. 1950	20 F	1.1962	1.2117	0.0155	0.0037	1.3	0.3
	15 NF	1.1272	1.1390	0.0118		1.0	
15 cities	20 F	0.9861	1.0020	0.0158	0.0034	1.6	0.3
	15 NF	0.9344	0.9469	0.0124		1.3	

5.16 Again the differences in the trends were small and not statistically significant.

KINLEN AND DOLL, 1981

5.17 The previous study by these authors (para 5.9-5.10) had been criticised by Yiamouyiannis (Winner et al., 1978; Yiamouyiannis, 1979) for its use of year-specific reference rates. Kinlen and Doll therefore repeated their analysis using single standard populations; in order to explore the effect of choice of standard they undertook a series of analyses, throughout each analysis using one of four reference rates, namely United States 1950, 1960, 1970, or the pooled cancer mortality rates of the 20 cities in 1970. They compared the results with those of an analysis using year-specific rates. The numerical errors in the earlier paper (Doll and Kinlen, 1977) were corrected.

5.18 A further criticism by Yiamouyiannis (1979) had been the inclusion of Atlanta and Seattle in the group of non-fluoridated cities in any analysis extending beyond 1968, as these two cities had fluoridated in 1969 and 1970 respectively. Kinlen and Doll therefore repeated all the analyses outlined above, but excluding Atlanta and Seattle from the set of non-fluoridated cities.

5.19 Yiamouyiannis and Burk (1977) had chosen their ten non-fluoridated cities on the basis of their crude cancer death rates in 1953 (see para 4.2). Kinlen and Doll argued that this was inconsistent with the choice of the fluoridated cities, which had been on the basis of size only; moreover, the selection of non-fluoridated cities with such a high crude cancer death rate could result in an atypically small rise in mortality rates in this group, because of the general tendency for extreme values to approach the average value over time. They therefore repeated all their analyses in a comparison of the ten fluoridated cities with the ten largest non-fluoridated cities.

5.20 The outcome of all the above analyses was a series of results from fifteen different bases of comparison, but the conclusion from each comparison was identical. In every instance, the percentage increase in SMR from 1950 to 1970 was slightly greater in the non-fluoridated cities than in the fluoridated cities. The conclusion from these authors' original study was unchanged.

5.21 Yiamouyiannis and Burk had criticised indirect standardisation, alleging that it could distort the results (Yiamouyiannis and Burk, 1977); they had preferred direct standardisation, although its proper application was not possible because the necessary data were lacking. Kinlen and Doll were also able to obtain appropriate data, for 1970 only, from the United States National Centre for Health Statistics. They found that the ratio (fluoridated/non-fluoridated) of the SMRs was identical to the ratio of the directly standardised mortality rates, irrespective of which set of non-fluoridated cities was chosen. Although it was only possible to undertake this comparison for 1970, it provided a strong indication that the use of direct standardisation based on narrow age-groups, and accounting for sex and ethnic group, would not be likely to lead to a different conclusion.

ANALYSES FOR THE WORKING PARTY — ALL CANCERS COMBINED (CHILVERS, 1983)

5.22 The principal study commissioned by this Working Party involved a re-examination of the data pertaining to the 20 cities, in the light of the controversies which had arisen regarding accuracy of data and matters of technique. The features of the reanalysis are listed below:

1. The data were transcribed independently, from 'Vital Statistics of the United States', and reports of the United States Census.
2. Independent checks on the fluoridation status of the cities were made.
3. The trends of the average crude cancer death rates for the original sets of fluoridated and non-fluoridated cities were calculated; the trends for the individual cities were also examined.
4. The effects of estimation of intercensal populations by linear interpolation were explored.
5. Various alternative sets of fluoridated and non-fluoridated cities were compared, namely:
   i   the original 20 cities (with or without Kansas City, which had fluoridated 1962-64);
   ii Taves's selection of 20 fluoridated and 15 non-fluoridated cities (see paragraph 5.15);
   iii Taves's selection of 20 fluoridated cities, and his 15 non-fluoridated cities less 4 which had fluoridated briefly during the period under consideration (Kansas City, San Diego, Seattle and Atlanta).
6. Four reference populations were chosen to provide alternative standard rates for each set of indirect standardisations. The populations were US 1950, 1960, 1970, and the original 20 cities, 1970.
7. The use of mortality data from census years only was compared with the use of data from either one or two pericensal years combined with the census year.
8. The changes in average mortality rates for the two sets of cities were viewed in the context of the range of the changes in the individual cities within each set.

5.23 The results of the analyses relating to crude death rates and to linear interpolation estimates have been discussed in Chapter 4; only the results of the series of indirect standardisations are considered here.

5.24 The approach adopted in the calculation of the average SMRs differs in one respect from that used in other studies considered previously in this chapter. In those, a single SMR was calculated for each set of cities at each census year, by adding all the 'observed' cancer deaths in all the cities of the set, and dividing by the sum of the 'expected' deaths. This procedure is equivalent to calculating an average of the individual cities' SMRs weighted by the expected deaths. In the commissioned study, however, SMRs were first calculated separately for each city in a set, then added together and divided by the number of cities; that is, an equally weighted average SMR was used. This was done in order to allow a calculation of the statistical significance of any difference found which would take proper account of the range of trends for the individual cities in each group.

5.25 The results of one series of analyses are given in Table 5.6 below.

Table 5.6 Standardised mortality ratios for the original 20 cities, using mortality data from censal and pericensal years; standard rates from U.S. 1960 population. Data from Chilvers, 1983. (Small discrepancies within this table result from the rounding of numbers).

Years used for mortality data	Set of cities	Average SMR		Increase in average SMR (b-a)	Difference of increase F — NF	% Increase $\frac{b-a}{a} \times 100$	Difference of % increase F — NF
		1950 (a)	1970 (b)				
Censal year	F	1.2054	1.2384	0.0330	−0.0009	2.7	−0.2
	NF	1.1680	1.2018	0.0339		2.9	
	Set of cities	Average SMR		Increase in average SMR (b-a)	Difference of increase F — NF	% Increase $\frac{b-a}{a} \times 100$	Difference of % increase F — NF
		1949-50 (a)	1969-70 (b)				
Censal year and one preceding year	F	1.2011	1.2324	0.0313	0.0073	2.6	0.5
	NF	1.1633	1.1873	0.0240		2.1	
	Set of cities	Average SMR		Increase in average SMR (b-a)	Difference of increase F — NF	% Increase $\frac{b-a}{a} \times 100$	Difference of % increase F — NF
		1948-50 (a)	1968-70 (b)				
Censal year and two preceding years	F	1.1819	1.2453	0.0634	0.0322	5.4	2.7
	NF	1.1530	1.1843	0.0312		2.7	

5.26 All of the comparisons yielded differences of similar magnitude between the average trends in the fluoridated and non-fluoridated cities. All of these differences were small in comparison with the wide range of trends within the two sets of cities (see Figure 5, which relates to the first of the three comparisons in Table 5.6), and none approached statistical significance.

5.27 There was thus no evidence of any difference between the average mortality trends in the two sets of cities, fluoridated and non-fluoridated, that could not easily have arisen by chance, and therefore no evidence of an association between fluoridation and cancer mortality. This conclusion was not affected by the choice of reference population or of the number of pericensal years; nor was the inclusion or exclusion of cities which had been fluoridated for under two years in the set of non-fluoridated cities of any consequence.

ANALYSES FOR THE WORKING PARTY — SPECIFIC CANCERS (CHILVERS, 1982)

5.28 Almost without exception, the studies discussed so far in this and the preceding chapter were based on the data for deaths from all cancers combined; the exception is the subsidiary analysis by Yiamouyiannis and Burk (1977) of crude death rates for three groups of cancers (see para 4.10.) The mortality rates for specific cancers in the 20 cities had not therefore been adequately examined. If fluoride caused cancer, and if it were analogous to known chemical carcinogens, it would act preferentially at one or a few particular sites in the body, but not at all sites equally. It was therefore possible that the analyses of all cancers combined could conceal an effect on a particular type of cancer. We considered it important to investigate this possibility.

5.29 It was not possible for the investigation to be carried out in as much detail as is desirable since only limited data were available (Chilvers, 1982). However, numbers of deaths were analysed for seven broad groups of sites (cancers of the digestive organs and peritoneum, respiratory system, breast, genital organs, urinary organs, leukaemias, and 'other malignant neoplasms').

5.30 Population numbers for intercensal years were not known for most of the cities, and therefore the study was centred on census years. The usual comparison, based on 1950 and 1970, was not possible because the volumes of 'Vital Statistics of the United States' did not contain site-specific data prior to 1953; it was therefore only feasible to compare 1960 and 1970 rates. Although both of these years are 'post-fluoridation', consideration of the usually long latency of cancer makes it unlikely that any effect of fluoridation on cancer would be evident as early as 1960, although it might be apparent by 1970.

5.31 The relatively small numbers of deaths from certain of the groups of cancers in some cities made the use of a single year's data unreliable, so data were aggregated for five years centred on each census year. The final form of comparison, therefore, was between SMRs for 1958-62 for 1968-72.

5.32 The average SMRs were calculated in the manner previously noted (see para 5.24). Two series of analyses were undertaken using reference rates from two alternative populations: US 1960 and US 1970.

5.33 The trends for individual cities were strikingly consistent, for most of the groups of cancers (Chilvers, 1982). Substantial differences between the trends for individual cities were seen only for urinary tract cancers and leukaemias.

5.34 For all cancers combined, and for five of the seven groups of cancer sites, the average SMR increased more (or decreased less) in the non-fluoridated cities. The SMR for leukaemias however, decreased less in the fluoridated cities, and the SMR for 'other malignant neoplasms' increased more in these cities. Neither of these latter differences was statistically significant. The only statistically significant difference was the greater decrease of the SMR for genital cancers in the fluoridated cities.

5.35 As Hoover et al (1976), in one of their four analyses of site-specific data, had found an apparent association between fluoridation and stomach cancer in males,[1] and as some other smaller studies (Heasman and Martin[2],

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1. See para 6.26.
2. See para 7.4.

1962; Okamura and Matsuhisa[3], 1967) could also be interpreted as possible evidence for such an association, special attention was paid to digestive tract cancer, of which stomach cancer is a major component. Digestive tract cancers in fact declined in both sets of cities, and the decrease was greater in the fluoridated cities. This contrasts with the opposite finding of Yiamouyiannis and Burk (1977), and emphasises the inadequacies of their analysis, based on crude rates only.

5.36 These data, therefore, did not provide any evidence that fluoridation was associated with an increase in mortality from cancer of any specific site.

DISCUSSION OF STUDIES CONSIDERED IN CHAPTER FIVE

5.37 Oldham and Newell (1977) demonstrated clearly that the demographic structures of the two sets of cities were quite different in 1950, prior to fluoridation, and moreover that the differences became more marked by 1970. It is not surprising that the crude cancer death rates should have diverged also. Although the sets of cities differed in other respects too — for instance, in their level of industrialisation (Strassburg and Greenland, 1979) — the crucial importance of taking population structure into account becomes obvious when standardisation is correctly applied. The remaining difference between the trends in cancer mortality is then so small as to be insignificant, either statistically or biologically. This is particularly clear when the difference is viewed in the context of the range of the individual trends in the 20 cities (Chilvers, 1983).

5.38 One of the objections of Yiamouyiannis concerned the use of data for 1970, because certain of the non-fluoridated cities (namely, Atlanta and Seattle) had in fact been fluoridated by 1970, although for under two years. Almost all cancers fatal in a particular year must have existed for more than two years; indeed, most of them must already have been diagnosed more than two years before the deaths occurred. It is therefore unlikely that any chemical could alter the mortality from all cancers combined in such a brief period. As would be expected, exclusion of Atlanta and Seattle from the non-fluoridated set has little effect (Kinlen and Doll, 1981; Chilvers, 1983). Similarly, examination of other cities (Taves, 1979) and expansion of the original 20 cities to 35 (Taves, 1979; Chilvers, 1983) does not change the conclusions.

5.39 Although Yiamouyiannis was later to use a form of indirect standardisation, he had claimed originally that it was an unreliable technique (Yiamouyiannis and Burk, 1977) and that direct standardisation was preferable. While there could, in theory, be important discrepancies between results obtained by the two types of standardisation, they would arise only if the populations under study had very unusual demographic structures which are most unlikely to occur in practice in large populations, and do not do so here. In a direct comparison of the two methods as applied to cancer mortality in the 20 cities in 1970, Kinlen and Doll (1981) found that they gave identical results. There were no grounds for Yiamouyiannis's objection.

5.40 The precise techniques used for the indirect standardisations discussed in this chapter have varied, for example in the number of pericensal years data used, and the method of averaging (equally weighted or otherwise). It is striking that none of these many analyses has shown any real differences between the trends of cancer mortality for fluoridated and non-fluoridated cities.

3. These authors speculated on the possibility of a relationship between the fluoride content of traditional Japanese food and the incidence of stomach cancer in Japan.

5.41 The examination of the cancer mortality rates for the twenty largest fluoridated cities, and the fifteen largest non-fluoridated cities, in the United States therefore provides substantial reassurance of the safety of fluoridation over almost two decades. Nineteen of the cities had been fluoridated for between 13 and 19 years by 1970 (Chilvers, 1983). The combination of rates for all types and sites of cancer does, however, carry with it the disadvantage that an important alteration in the rates of any one specific cancer (or group of cancers) may not be detected. Although the data for the original sets of fluoridated and non-fluoridated cities did not permit the ideal investigation to be made, there was no indication from the available data that any effect of fluoridation on specific cancers was being obscured (Chilvers, 1982).

CONCLUSIONS TO CHAPTER FIVE

5.42 Reanalysis of the cancer mortality rates of the ten fluoridated and ten non-fluoridated cities chosen by Yiamouyiannis and Burk (1977) provides no evidence that fluoridation has affected mortality from cancer in general.

5.43 The conclusion is unaltered by valid variations of analytical technique, or by different valid choices of cities, reference rates, or (within limits) the number of pericensal years used.

5.44 The examination of mortality rates for cancers of specific sites does not indicate any effect of fluoridation on any specific cancer.

CHAPTER 6

OTHER STUDIES IN THE UNITED STATES

INTRODUCTION

6.1 The analyses of the '20 United States city' data and of allied data, discussed in the preceding two chapters, represent only some of the many studies which have been conducted on data from the United States. In the present chapter, studies of other data are described in three groups. The first group comprises comparisons of cancer mortality in areas with different concentrations of fluoride occurring naturally in drinking water. The studies in the second group are comparisons of cancer mortality of morbidity in areas following fluoridation and in non-fluoridated areas at the same time. The third group consists of studies which examined the trends in cancer mortality over time, in relation to fluoridation of water.

COMPARISONS IN AREAS WITH DIFFERING NATURAL LEVELS OF FLUORIDE

6.2 The earliest American reference to cancer mortality in man, in relation to fluoride in water, occurs in a commentary by E Taylor (1951) on reports of experiments (later published by A Taylor, 1954) which appeared to demonstrate a positive association between mammary tumours in mice and the fluoride level in their water supply. E Taylor described several criticisms of the experiments, and cited another study in mice, with opposite findings. He stated that <u>human</u> breast cancer rates in thirteen Texas cities were lower in those areas with a high level of fluoride in the water than in those with practically no fluoride. The author also stated that the average rate of breast cancer in the United States was about 13 per 100,000, compared with 17 per 100,000 in five New England States with practically no fluoride in the water supplies, and only 7.3 per 100,000 in Texas as a whole, where "there is no more fluoride in the water supplies than in any part of the country".

6.3 Such a report can only be regarded as preliminary. The rates are presumably not adjusted for demographic factors, nor is it clear whether they refer to incidence or mortality.

6.4 In the early studies, it was usual for cancer to be included as one of the several major disease categories for which mortality statistics were collected routinely. Thus, the Department of Public Health of the State of Illinois published a report (Illinois, 1952) which examined the risk of death from heart disease, cancer, nephritis and diabetes, in addition to the combined mortality from all causes. These mortality statistics for 1940 for the four Illinois cities with over 10,000 inhabitants and a natural content of fluoride in water of over 0.7 ppm (respectively 0.8, 1.1, 1.2 and 2.0 ppm) were compared with those for a random sample of 18 'non-fluoride' cities of similar size in the State (with an average fluoride content in water from 0 to 0.4 ppm). The use of local statistics permitted age-standardised rates to be calculated, applying the direct method to 5-year age-groups for adults, but taking both sexes and all races together. The average of the age-standardised mortality rate for cancer (without weighting for size of city) was greater for the 'fluoride' cities (140 per 100,000) than for the 'non-fluoride' cities (129.5 per 100,000). The rates for individual cities ranged widely (from 91.3 to 183.9) and the range in the group of 'fluoride' cities was similar to that in the group of 'non-fluoride' cities. The authors indicated that the group differences were not statistically significant (though no test results were quoted) and concluded that "it seems highly improbable that the risk of death is increased by drinking fluoridated [sic] water." However, the 'fluoride' group was small and further information would be required for a fuller assessment.

6.5 In 1954 Hagan, Pasternack and Scholz published a more extensive comparison of mortality rates from several diseases. Each of thirty-two United States cities with a population of 10,000 or more in 1950 and with a high natural level of fluoride in the water supply (each city having more than 0.7 ppm in the majority of analyses, and up to 4 ppm) was paired with the nearest low-fluoride city of similar size in the same State (each city with no more than 0.25 ppm fluoride). The average of the cancer death rates for 1949-50, indirectly standardised for age, race and sex, was 135.4 per 100,000 for the high-fluoride group, slightly lower than that for the low-fluoride group (139.1). In sixteen of the thirty-two pairs the rates were lower in the high-fluoride city, and in sixteen they were higher. There has been considerable discussion about the appropriate methods of analysing these data (Yiamouyiannis, 1979; Maritz, 1980; Maritz and Jarrett, 1983), but none of the alternative approaches demonstrates a significant difference in cancer mortality between the two groups of areas.

6.6 Knutson (1954) summarised what appears to be a variant of the same study, comparing mortality in a group of 28 high-fluoride cities and in a geogrpahically matched group of 60 low-fluoride cities. He noted that the cancer mortality rates, standardised for age, sex and race, were below the median for the entire group of eighty-eight cities in fifteen of the twenty-eight high-fluoride cities, and above the median in thirteen.

6.7 Leone *et al* (1955) compared the towns of Bartlett (with a natural level of fluoride of 8 ppm) and Cameron (fluoride level of 0.4 ppm). Individuals were examined clinically and radiologically in 1943, and again ten years later. There was no significant difference between the incidence in the two towns of "tumour and/or cysts" (nor of any other disease examined); but the numbers involved were small, and more precise diagnoses were not given.

6.8 The water supply of Colorado Springs had a natural level of fluoride of about 2.5 ppm. Geever *et al* (1958) between 1947 and 1953 conducted 728 post-mortem examinations in this area, on subjects aged 10 or over. They were unable to demonstrate any consistent increase in the proportion of findings of cancer (or any other detectable disease) with increasing length of residence in the area.

6.9 The initial reports by Burk and Yiamouyiannis (Burk and Yiamouyiannis, 1975) were based on certain of the average cancer mortality rates for the United States counties from 1950 to 1969. (These studies are discussed in Chapter 3). The data used by Burk and Yiamouyiannis had recently been compiled and published by the Epidemiology Branch of the United States National Cancer Institute (Mason and McKay, 1974). Hoover, McKay and Fraumeni, from the Epidemiology Branch, subsequently published their own studies of mortality rates in United States counties (Hoover *et al.*, 1976). One of the four investigations reported in the paper considers cancer mortality in relation to natural levels of fluoride. Fifty-three counties of Texas were divided into four groups according to the natural level of fluoride in water (less than 0.7 ppm, 0.7-1.2 ppm, 1.3-1.9 ppm, 2.0 ppm or more). Standardised mortality ratios (SMRs) for white males and white females were calculated for the entire twenty-year period (1950-69); in this analysis the counties were first grouped according to their level of urbanisation and social class, and the 'expected' number of deaths was calculated for each group separately. SMRs were tabulated separately for all cancer sites, and for thirty-four individual sites, including those specifically implicated by Yiamouyiannis (Yiamouyiannis, 1975(d); Burk and

Yiamouyiannis, 1975). Multiple regression analyses were also performed, including the urban population percentage, the median years schooling completed by adults, percentage non-white, and percentage foreign stock as indpendent variables, to allow more fully for urbanisation and other socioeconomic factors. The weighted average fluoride concentration for each county was then included in the regression, to assess its importance as an additional 'explanatory' variable. These comprehensive analyses revealed no consistent positive association of cancer mortality with the natural level of fluoride, for all sites combined, for any of the sites under particular suspicion, or for any other individual site.

6.10   Austin (1975) also used the 'county data' in an examination of the 1950-69 mortality from the seven specific cancers which had been alleged by Yiamouyiannis (Yiamouyiannis, 1975(d); Burk and Yiamouyiannis, 1975) to demonstrate increased cancer mortality for white males in fluoridated areas. The cancers concerned were those of the tongue and mouth, oesophagus, stomach, large intestine, rectum, kidney, and bladder (see paras 3.26 *et seq*). Austin compared all the counties with drinking water concentrations of at least 5 ppm fluoride for a significant portion of the population of the county (usually over fifty percent) with a group of 'low-fluoride' counties (with an average of no more than 0.7 ppm fluoride). The twenty-year average annual age-adjusted cancer mortality rates for white males and females separately were found to be similar in both groups of counties; only one comparison (cancer of the oesophagus in white females) showed a minimal disadvantage to the 'high-fluoride' counties. Austin concluded that "the hypothesis that fluoride causes cancer is rejected".

COMPARISONS OF CANCER RATES FOR A SINGLE PERIOD IN FLUORIDATED AND NON-FLUORIDATED AREAS

6.11 Kinlen (1974, 1975) published a preliminary investigation of crude incidence rates for cancers of thyroid, kidney and bladder, in four areas of New York State and four areas of Connecticut. The rates were all greatest in the non-fluoridated areas. The author acknowledged, however, that the age-structure of the populations being compared were different (Kinlen, 1975).

6.12 The remaining studies considered in this section were all published from 1975 onwards, and were conducted in response to the claims of Yiamouyiannis and Burk. Thus, Hoover *et al* (1976) carried out a multiple regression analysis of the 1950-69 data for the twenty counties considered by Burk and Yiamouyiannis (1975). Yiamouyiannis (1975d; Burk and Yiamouyiannis, 1975) had claimed that cancer in nine sites (namely, breast, ovary, tongue and mouth, oesophagus, stomach, large intestine, rectum, kidney, and bladder) was adversely affected by fluoridation (see paras 3.26 *et seq*). Hoover and colleagues examined the cancer mortality for those sites, both before and after adjusting for the following demographic and socioeconomic factors: — population density, median years schooling of the adult population, per cent employed in manufacturing industries, percent non-white, percent foreign stock, and geographic region. If these factors were not taken into account, fluoridation appeared to be an important factor contributing to a high mortality, but when they were, there was only one remaining statistically significant association. This was with stomach cancer. Stomach cancer is known to be particularly common in certain ethnic groups, and when ethnic group was also allowed for the association with fluoride was partly, although not entirely, resolved. There was still a residual association, limited to males. Hoover and his co-authors concluded that almost all of the elevated cancer mortality rates previously described by Burk and Yiamouyiannis for artificially fluoridated areas could be traced to differences in the distribution of demographic and socioeconomic risk factors in the

fluoridated and non-fluoridated areas. However, the findings on stomach cancer might constitute an important exception, and this possibility demands special attention. We discuss it later, in paragraph 6.26.

6.13 Austin (1975), in his second examination of data on cancer of seven of the nine cancer sites implicated by Yiamouyiannis, analysed the age-adjusted cancer mortality rates reported by Mason and McKay (1974) for white males and females for the entire period 1950-69. The mortality rates were compared in 21 selected counties in California, nine with 'high' fluoride levels (range 0.1-7.2 ppm) two with 'intermediate' fluoride levels (0.1 to 1 ppm), and ten with 'low' fluoride levels (0.1 ppm or less). The rates for either sex were similar in the low-fluoride and high-fluoride groups, for each site (including stomach cancer), but all the rates were highest in the 'intermediate' group. There was therefore no evidence to relate cancer mortality to fluoride levels.

6.14 The fluoride in the Californian 'high-fluoride' counties examined by Austin was principally from natural sources. The majority of the population of the 'intermediate' counties, however, lived in the artificially fluoridated county of San Francisco. Austin therefore continued with a comparison of San Francisco County itself, the remaining artificially fluoridated vicinities within the San Francisco Bay Area Counties, and the non-fluoridated vicinities. He calculated the age-adjusted rates of cancer incidence for 1972-3 (using data from the California Tumor Registry), in white males and females, and for the same seven sites of cancer. In this small study, it was clear that the incidence rates were generally higher in San Francisco County than in either of the other groups of vicinities, in which the rates were similar to each other; however, none of the differences was statistically significant. Austin concluded that "none of the above data supports the hypothesis that the fluoride ion, in concentrations found in drinking water, is causally related to or is associated with cancer incidence or mortality of any of the investigated sites".

6.15 Yiamouyiannis (1975a, b, c) had previously implied that the high cancer death rate in San Francisco was a consequence of fluoridation. Austin (1975) pointed out that the incidence and death rate from cancer in San Francisco had already been high in 1948, five years before fluoridation. Further, Newbrun (1977) demonstrated that the increase in the crude cancer death rate which subsequently occurred in that city was simply the effect of an ageing population; standardisation for age eliminated the trend.

6.16 Erickson (1978) compared mortality rates for a wide range of diseases in twenty four 'fluoridated' cities and twenty two 'non-fluoridated' cities with populations of 250,000 or more in 1970. The 'fluoridated' cities were defined as those with a water fluoride level of 0.7 ppm or greater, whether this was present naturally, or had been artificially added. Cities whose supplies were first fluoridated in 1965 or later were excluded. Death rates were tabulated for white and black populations combined, for the three-year pericensal period 1969-71. The crude death rates for cancers of all sites combined were 206.6 per 100,000 in the 'fluoridated' cities and 183.0 per 100,000 in the non-fluoridated cities, but indirect standardisation for age, race and sex reduced the difference (per 100,000) from 23.6 to 7.6. Further adjustment, taking into account a number of indicators of the social structure of the cities (population density, median education, median income, and the percentage of the work force employed in manufacturing) abolished the remaining difference. Analyses of the mortality rates for seven groups of sites of cancer were likewise negative. A similar pattern was observed for all the diseases studied,

and Erickson concluded that "there was no evidence of a harmful effect, including cancer, attributable to fluoridation".

6.17 A survey of cancer mortality rates in white males and females, in counties in Kansas for the period 1973-77, was reported by Neuberger (1982). Age-standardised death rates for all cancers, and for eight specific sites, were compared in fluoridated and non-fluoridated counties. Neuberger concluded that "the Kansas data to not support any hypothesis linking artificial fluoridation with cancer."

STUDIES OF TRENDS IN CANCER RATES IN RELATION TO FLUORIDATION OF WATER

6.18 The early fluoridation schemes in the United States were accompanied by programmes to monitor the health of the trial communities. There was no reason to suggest cancer specifically as a possible hazard of fluoridation, nor to expect that cancer mortality rates would be altered in the first few years after fluoridation. Cancer was therefore mentioned in only a few of the early studies, and then only briefly. Schlesinger *et al* (1956), for instance, reported that there was no increase in the crude cancer death rates in the ten years following fluoridation in Newburgh (New York State), in comparison with the similar nearby non-fluoridated community of Kingston; the analysis was not carried further.

6.19 Swanberg (1953), commenting on claims by Perkins (1952) that fluoridation had increased the <u>number</u> of cancer deaths in Grand Rapids, Michigan, noted that there was a decrease in the crude cancer death <u>rate</u> after eight years fluoridation, whereas there had been an increase in rate in the United States as a whole. Although Swanberg was concerned principally to demonstrate that numbers of deaths (rather than mortality rates) are misleading, he indicated that it would also be desirable to take into account the effects of an ageing population on cancer mortality.

6.20 Knutson (1954) took the analysis a stage further. He found that, when standardised for age, sex and race, the estimated annual cancer death rates for the years 1943 to 1950 were similar in Grand Rapids (fluoridated from 1945) to those in nearby non-fluoridated Muskegon, and that both sets of rates were greater than in the United States as a whole. Yiamouyiannis (1979) pointed out that the increase in cancer mortality specifically from the year 1945 to the year 1950 was greater in Grand Rapids than in Muskegon. However, inspection of the estimates for all of the years suggests that there was substantial year to year fluctuation in the estimated rates in these small areas, and that over the period as a whole, as distinct from the two selected years, the experience of the two areas had been similar.

6.21 Several other studies of time-trends were conducted in response to the claims of Burk and Yiamouyiannis. Hoover *et al* (1976) calculated the cancer mortality rates, for males and females separately, in those 61 United States counties that had fluoridated their water supplies between 1950 and 1964, and in 156 counties which had not fluoridated their supplies by 1970. The twenty-year period 1950-69 was divided into four successive five-year periods (called 'pentads' by Hoover and his co-authors), namely 1950-54, 1955-59, 1960-64, 1964-69. Age-standardised cancer death rates and summary SMRs were calculated for all cancer sites combined, and for thirty-four separate sites of cancer. The ratio of the mortality rates for the fluoridated counties to those for the non-fluoridated counties was determined for each pentad. There was no increase in the ratio with time, and in particular, no increase from pre-fluoridation pentads to post-fluoridation pentads; and there were no consistent trends when individual cancer sites were considered.

6.22 Hoover *et al* (1976) also conducted a small study of the trends in age-standardised cancer <u>incidence</u>, by sex and site, between the Second National Cancer Survey in 1947-8 and the Third National Cancer Survey in 1969-71. Denver, where extensive fluoridation commenced in 1954, was compared with Birmingham (Alabama), where there was little fluoridation until *after* 1970. There was no evidence of consistent upward or downward trends in the ratios of the morbidity rates for Denver to those for Birmingham.

6.23 Rogot *et al* (1978) investigated the trends in mortality from all causes combined, over the period 1950-1970, in 473 of the 484 United States cities with populations greater than 25,000 in 1950. The mortality rates from cancer and from heart disease were also studied separately. After excluding 33 cities with uncertain fluoridation status, and 26 with *natural* levels of fluoride ranging from 0.7 to 2.7 ppm, there were 227 cities which had fluoridated between 1945 and 1969, and had remained fluoridated throughout the remainder of that period, and 187 cities which had not fluoridated by 1970, and were using water with an average natural level of fluoride of under 0.7 ppm. Pericensal cancer mortality rates (around the census years of 1950, 1960 and 1970) were standardised for age, race and sex, by the indirect method. Average SMRs (equal weights) were then calculated for the two groups of cities, fluoridated and non-fluoridated. No relationship was observed between fluoridation and changes in cancer mortality over the twenty-year period. Preliminary analyses, in which the averages had been weighted by city size, were stated to have yielded similar results.

DISCUSSION OF STUDIES CONSIDERED IN CHAPTER SIX

6.24 In the early years of fluoridation, the only reasonable way to study the effect of fluoride in drinking water on human cancer rates was by the comparison of populations who had been drinking water containing high or low levels of naturally occurring fluoride for many decades. Those studies would be expected to reveal an effect, if one existed. The paper by Hagan *et al* (1954) found no evidence of an effect; the later study of Texas counties by Hoover *et al* (1976) provided further reassurance.

6.25 The comparison of populations over the years, before and after the introduction of fluoridation, provides a direct method of examination for any effects of fluoridation. Such studies of cancer rates and their trends in the United States now cover a large number of communities and provide results for up to 25 years following fluoridation for some communities, without any sound evidence of harm (Hoover *et al*, 1976); Rogot *et al*, 1978; Erickson, 1978). The consistency of the results from the studies, reviewed here and in Chapter 5, is striking.

6.26 Only one apparent positive association between fluoridation and cancer emerged from all the United States studies. In one of the four investigations reported by Hoover *et al* (1976) there was a relationship with cancer of the stomach in males.

There was no such association in females, nor in either males or females in any of the three other studies reported in the same paper. None of the studies by other authors referred to in this chapter, and which specifically considered stomach cancer (Austin, 1975; Erickson, 1978; Neuberger, 1982) found any such association. The single finding by Hoover and colleagues therefore seems to be quite isolated, and can be interpreted with confidence as a 'chance' effect. This statement is supported by the fact that cancer of the stomach in recent decades has exhibited a consistent decline in incidence and mortality in the United States, over a period which saw the introduction and spread of fluoridation. (See also paras 5.35 and 7.4).

6.27 Various criticisms have been made of the methods used in several of the studies, in terms, for example, of the small numbers of areas studied, the small total populations, the way in which samples have been selected from the available material, or the techniques of analysis. Although some of these criticisms are justified in relation to individual studies, the impact of these shortcomings on the interpretation of the results is not great. There is no reason to suspect that deficiencies in design or analysis in these studies have obscured any real excess of cancer mortality or cancer incidence in fluoridated areas or others with moderate or high levels of fluoride present naturally.

CONCLUSION TO CHAPTER SIX

6.28 Neither the more general early studies, undertaken at a time when there was no specific suggestion of an association between the level of fluoride in the drinking water and cancer incidence or mortality, nor the more specific later studies, undertaken in response to the claims of Yiamouyiannis and Burk, provide any sound evidence of a short-term or long-term cancer hazard from fluoride in drinking water, whether this had been added to achieve a level of about 1 ppm in a fluoridation scheme or whether it occurred naturally, sometimes at a much higher level. No consistent evidence of a hazard has been found either in terms of cancer in general, or in terms of cancer at any of a number of specific sites.

CHAPTER 7

STUDIES IN THE UNITED KINGDOM

INTRODUCTION

7.1 As in the United States, the initial studies of the effects of fluoride in water on populations in the United Kingdom depended on examinations of indices of diseases (including cancer) for areas with differing levels of naturally-occurring fluoride. After fluoridation began, comparisons between fluoridated and non-fluoridated areas were made, and trends in the mortality and incidence of cancer were compared in these areas.

COMPARISONS IN AREAS WITH DIFFERING NATURAL LEVELS OF FLUORIDE

7.2 The earliest study in the United Kingdom to mention cancer (Weaver, 1944), was based on the crude mortality rates for 1930-39 in South Shields and Tynemouth, in which the natural levels of "fluorine" in water supplies were approximately 1.4 ppm and "less than 0.25" ppm respectively. No details were given, other than for all causes of death combined, but Weaver stated that "for most of the major causes of death, such as heart disease, malignant disease, cerebral haemorrhage and nephritis, the rates for the two towns were approximately the same".

7.3 The first detailed study in the United Kingdom dealt with mortality from various causes, including cancer (Heasman and Martin, 1962). It was modelled on the United States study by Hagan *et al* (1954), discussed in para 6.5. Eighteen urban areas each with average fluoride levels of 0.4 ppm or over were individually matched with similar adjacent areas with levels of less than 0.2 ppm; the levels defining 'high' and 'low' fluoride areas were necessarily lower than in the United States study. The death rates aggregated for the whole period 1950-59 were standardised by the indirect method for age and sex, and the resulting standardised mortality ratios (SMRs) were compared for the 'high-fluoride' and 'low-fluoride' areas, for the greater part separately for Northern and for Southern regions. The SMR for all cancers combined (excluding stomach, lung and leukaemia, which were considered individually) was significantly higher in the 'low-fluoride' areas in the Southern regions (p<0.05), but virtually identical in 'high-fluoride' and 'low-fluoride' areas in the Northern regions.

7.4 Heasman and Martin reported that the average SMR for cancer of the stomach for the three 'high-fluoride' areas in the Northern region was greater than the average for the two Northern 'low-fluoride' areas. They reported that the difference between the average SMRs was 'statistically significant', but it is probable that the test used did not fully take into account the range of SMRs for the five individual areas included in the Northern region. There was no association between fluoride level and stomach cancer mortality in the Southern areas. Heasman and Martin concluded that therefore "the difference in fluoride levels is most unlikely to have been the cause of the difference in mortality". As we shall see, later investigations by other authors in the United Kingdom have shown no evidence of an effect of fluoride in water on the mortality from, or incidence of, stomach cancer, and Heasman and Martin's finding can be interpreted as a 'chance' effect. (see also paras 5.35 and 6.26).

7.5 Nixon and Carpenter (1974) reanalysed cancer mortality data for the urban areas studied by Heasman and Martin (1962). They were able to use the data for a longer period (1950-65) and to take into account socioenvironmental factors. Although they did not consider stomach cancer separately, they found no significant association between the fluoride content of water and the standardised mortality ratios from 'diseases of the stomach' (a category which included stomach cancer). They also examined the mortality from all cancers combined, and found a negative, though not statistically significant, correlation between SMRs and water fluoride content. Their conclusions were not altered by the exclusion or inclusion of the socioenvironmental factors.

7.6 The water data on which these two studies were based were checked for the Working Party (Conway, personal communication). Three of the 'high-fluoride' areas (Wivenhoe, Maldon MB and Haverhill) had been assigned inappropriately high average fluoride levels; in one of these (Haverhill) the actual levels were always less than 0.4 ppm. One of the 'low-fluoride' areas (East Dereham) had an actual average level of over 0.5 ppm, but this appears to have been taken into account by Nixon and Carpenter (1974). It seems unlikely that these errors have distorted the results to an appreciable extent.

7.7 Kinlen (1974, 1975) considered the incidence of cancers in nine organs. Some of the sites appear to have been chosen because, from the knowledge, at that time, of the metabolism of fluoride, any effect of fluoride on cancer might have been anticipated at those sites (thyroid, kidney, bladder, bone); other more common sites of cancer were also included in the study (breast, oesophagus, stomach, colon, rectum). Kinlen used data for the years between 1961 and 1968, from the National Cancer Registration Scheme of the Office of Population Censuses and Surveys. Seventeen high-fluoride areas (average of 1 ppm or more), were matched with an equal number of low-fluoride areas (0.2 ppm or less) and 31 medium-fluoride areas (average of 0.5-0.99 ppm) were matched with very low-fluoride areas (0.1 ppm or less). The areas with the lower levels of fluoride were selected from amongst those near to an area with the appropriate higher level of fluoride; urban areas were matched with urban areas, and rural with rural. After standardisation for age and sex, the average Standardised Registration Ratio (SRR) for each cancer site, for the high-fluoride areas, was compared with the corresponding SRR for the low-fluoride areas; similarly, the medium-fluoride areas were compared with the very low-fluoride areas. There was no cancer site for which the high- and medium-fluoride areas had an SRR that was significantly greater than that for the low- or very low-fluoride areas respectively. No test results were quoted, but the Working Party has confirmed that this statement was correct.

7.8 In view of the importance of Kinlen's study to the issue of fluoridation in the United Kingdom, the Working Party decided to re-examine his data. Dr Kinlen kindly provided us with all the original reports and correspondence with water boards. From a reassessment of the water data (Conway, personal communication) it appeared that the fluoride classification of some localities required revision. The discrepancies had arisen because of the complex nature of the water supply in some areas and the paucity of early data. Kinlen's study was therefore repeated for the Working Party, excluding the misclassified areas but including some additional areas. It was possible to use more detailed information on water fluoride levels, and more recent cancer incidence data (1969-73), including data for all cancers combined and for several additional sites of cancer. Details are given in Appendix 3.

7.9 The age-standardised registration ratio (SRR) for all cancers combined was <u>smaller</u> for the areas with relatively high levels of fluoride than for the areas with relatively low levels of fluoride, for males and for females. When the SRRs for cancers of specific sites were examined, the only statistically significant differences were in the same direction — that is, the SRR was smaller for the areas with relatively high levels of fluoride. The only exception was the category of 'other skin cancers', for which the SRR was greater for both sexes in the higher-fluoride areas. Data on the incidence of such cancers, however, are especially unreliable, as cancers in this category usually cause no untoward symptoms and often have an excellent prognosis; they frequently go undiagnosed and unregistered.

7.10 Mortality data, for the same areas and the same years as the cancer incidence study above, were also analysed for the Working Party (Chilvers and Conway, 1985). Data for cancers of twelve sites (buccal cavity with pharynx, oesophagus, stomach, intestine, rectum, pancreas, lung, skin, breast, ovary, bladder, kidney with other urinary cancers) were considered, in addition to the data for cancers of all sites combined. The mortality rates were age-standardised, for males and females separately.

7.11 There were only four statistically significant differences between the SMRs in the paired groups of areas (high and low-fluoride; medium and very-low fluoride). The SMR for cancer of the buccal cavity and pharynx in females was significantly higher for the high-fluoride areas than for the low-fluoride areas, but the trend was in the other direction in males; there was no statistically significant difference between medium-fluoride and very low-fluoride areas for either sex for this site. For each of the remaining statistically significant differences ('all cancers' in men, male rectum and male bladder) the SMR was <u>lower</u> in the higher-fluoride areas in each comparison.

7.12 The few trends that were apparent in our analyses of cancer incidence and cancer mortality in the United Kingdom therefore seem to favour the areas with higher natural levels of fluoride, but this is more likely to indicate some dissimilarity between the areas other than in fluoride levels, rather than to indicate some benefit from fluoride in respect of cancer.

COMPARISONS OF CANCER RATES FOR A SINGLE PERIOD IN FLUORIDATED AND NON-FLUORIDATED AREAS

7.13 In addition to his study of cancer incidence in localities with different levels of naturally-occurring fluoride, Kinlen (1974, 1975) examined SRRs (standardised for age and sex) for the aggregate of three areas in which fluoridation schemes had been introduced (Anglesey, fluoridated in 1955. Watford, fluoridated 1956; Birmingham C.B. with Solihull M.B., fluoridated 1964), comparing them with the SRRs in adjacent non-fluoridated areas (less than 0.15 ppm fluoride). The SRRs for Anglesey and Watford related to the years between 1961 and 1968, but those for Birmingham and Solihull were for the period 1965-8 only. The SRR was somewhat higher in the fluoridated areas for six sites of cancer (thyroid, kidney, colon, rectum, bladder and breast); it was higher in the non-fluoridated areas for three sites (stomach, oesophagus and bone). Kinlen indicated that none of these differences was statistically significant.

7.14 Burk (1979a, b) reassessed this part of Kinlen's paper relating to artificial fluoridation in England and Wales. He combined the cancer incidence for those six sites of cancer (out of the nine) whose SRRs were somewhat higher in the fluoridated areas, and constructed thereby the appearance of a "very large" difference associated with fluoridation. Burk

claimed that "since cancer is fairly organ-specific with respect to external causative factors, a statistical separation of positive and non-positive indications is desirable and in fact called for". There is, however, no biological basis for his combination of cancers of thyroid, kidney, colon, rectum, bladder and breast, nor for the exclusion of stomach, oesophagus, and bone cancers. Selection of data which on prior inspection happen to support a particular hypothesis, and rejection of data which do not, is neither 'desirable' nor 'called for'. It is utterly unacceptable.

7.15 Burk (1979a, b) also compared the incidence data presented by Kinlen (1974, 1975) for the areas with fluoride naturally present in water (see para 7.7 above), with the incidence data for artificially fluoridated areas (see para 7.13). In this part of his papers, Burk used Kinlen's data to calculate the crude incidence rates. Burk pointed out that there was a "remarkably large discrepancy (about 60%)" between the combined crude incidence rates in these two sets of data, and that this difference was "largely independent of fluoride or fluoridation levels". In the example given by Burk, the three fluoridated areas together with their matched non-fluoridated areas have a crude cancer incidence rate of 238 per 100,000 for the six "positive" organs referred to previously. This is lower than the rate for the areas with various levels of naturally occurring fluoride (379 per 100,000).

7.16 This "discrepancy" is not surprising. Burk's illogical combination of data and his comparison of crude incidence rates, ignored the differences in cancer incidence at different ages, and for the two sexes. Our own calculations indicate that the average SSRs derived from the two sets of data presented by Kinlen were almost identical; Burk's "discrepancy" disappeared when the incidence rates were standardised. His analysis served only to demonstrate that crude cancer rates provide an unreliable basis for comparisons of human populations.

STUDIES OF TRENDS IN CANCER RATES IN RELATION TO FLUORIDATION OF WATER

7.17 Birmingham has been fluoridated since 1964, and has been the basis for a number of studies of fluoridation and cancer. Schatz and Schatz (1972), having first made it clear that they believed that "fluorine is among other things, a carcinogen", went on to state that "our analysis of official health statistics from Birmingham, England, show that the death rates from 'leukemia' and from all types of cancer were significantly greater from 1965 to 1969 than from 1958 to 1964". These statements were made without accompanying data or analyses.

7.18 Brady (1977) also commented on a "marked rise" in cancer deaths in Birmingham after 1964, and her graphical presentation of annual crude death rates from 1954 to 1973 showed an increase immediately following fluoridation. She concluded that "while this graph does not prove that fluoridation was responsible for all of the higher cancer death rates, it gives cause for great concern".

7.19 As a result of Brady's comments, Burk examined annual crude cancer death rates for Birmingham (Burk, 1980, 1981). He claimed that, following fluoridation in 1964, Birmingham showed the greatest increase in the crude death rate for cancer of any large city in the world. He stated (Burk, 1981) that he looked for "an abrupt change linked with the initiation of fluoridation". He therefore fitted two distinct lines to annual crude cancer death rates for relatively short periods before and after fluoridation, originally 1955-64 and 1964-77 (Burk, 1980). The difference between the slopes of these separate

Figure 6 Annual changes in the crude death rates from all
malignant neoplasms in the seven largest English cities
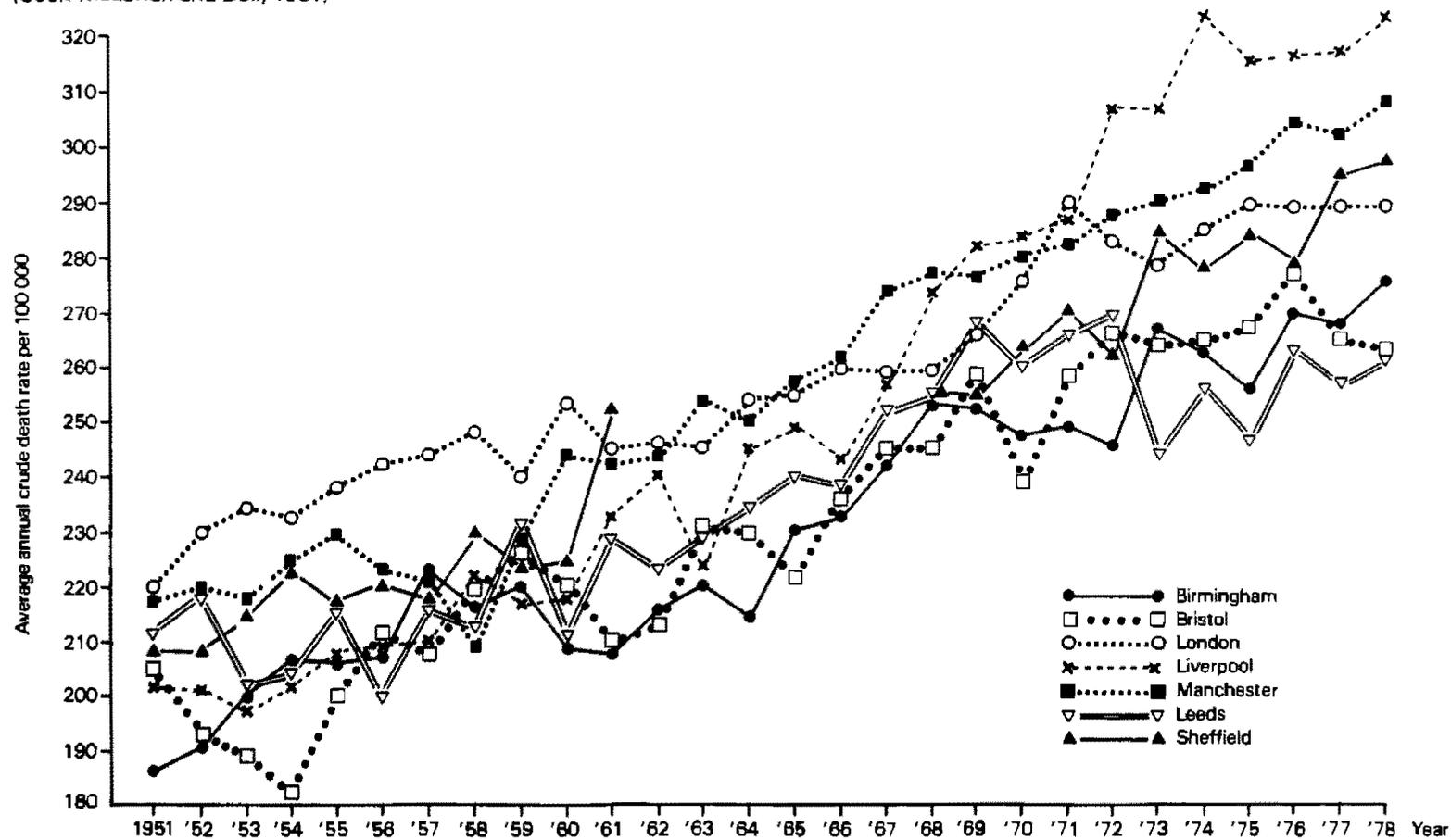(Cook-Mozaffari and Doll, 1981)

Table 7.1 Changes in SMRs for all Cancers Combined, for Fluoridated and Non-Fluoridated Areas. (Cook-Mozaffari and Doll, 1981).

	Birmingham and Solihull (fluoridated)	Rest of the West Midlands conurbation (non-fluoridated)
% change 1959-63 to 1969-73	+6.1	+9.0
% change 1969-73 to 1974-78	+1.0	-1.3
% change 1959-63 to 1974-78	+6.3	+8.2

7.23 In another paper, Cook-Mozaffari *et al* (1981) examined age-standardised mortality rates, for men and women separately, for Birmingham and for the six non-fluoridated cities in England with populations of over 400,000 in 1961 (London, Bristol, Liverpool, Manchester, Leeds and Sheffield). The periods studied were again 1959-63, 1969-73 and 1974-78. Care was taken that the statistics for population and cancer deaths were for the same areas, and that account was taken of the changes which had occurred in administrative boundaries and census registration practices. They found that the change in cancer death rates in Birmingham, either for all cancers combined, or for each of twelve sites (buccal cavity with pharynx, oesophagus, stomach, intestine with rectum, larynx, lung with bronchus, breast, cervix uteri, other uterine cancers, prostate, bladder, and leukaemia) was within the range of changes observed in the other six cities. The increase, from 1959-63 to 1969-73, in the rate for all cancers combined was identical in Birmingham (6.4%) to the average increase for the other six cities. The authors therefore saw ''no reason to suppose that any unique factor, such as fluoridation of the water supplies, has affected the death rate for cancer in Birmingham since 1964''.

7.24 Cook-Mozaffari and Doll (1981) gave some details of an examination by Wynne Griffith of SMRs for men and women in Anglesey, which has been fluoridated since 1955. There was an increase in cancer mortality of 11.1 percent between 1949-53 and 1959-63, but a decrease of 8 percent between 1959-63 and 1969-73. When cancers of the lung and bronchus were removed from the total, the early increase in other cancers was 1.8 percent, and the later decrease was 16.7 percent. Although such a study cannot be accepted as conclusive, there was no evidence here of the ''abrupt and sustained'' increase in cancer death rates which would have been expected if Burk's interpretation of the Birmingham data were correct.

DISCUSSION OF STUDIES CONSIDERED IN CHAPTER SEVEN

7.25 Some of the earliest studies relating to naturally occurring fluoride must be regarded as no more than exploratory, as the data were not extensive and the analysis not detailed (e.g. Weaver, 1944). However, the reanalysis and extension of the work of Heasman and Martin (1962) by Nixon and Carpenter (1974) supported Heasman and Martin's conclusion of the absence of an effect of fluroide on cancer.

7.26 The study by Kinlen (1974, 1975) of cancer incidence is both extensive and detailed. The Working Party's reanalysis, summarised in this chapter and in Appendix 3, incorporated a careful reassessment of the water data (Conway, personal communication), and supplemented Kinlen's study with data for further cancer sites, more recent years, and cancer mortality rates (Chilvers and Conway, 1985). Our results agreed with Kinlen's findings of the absence of any relationship between fluoride and cancer.

7.27 Kinlen also found no association between artificial fluoridation and

cancer incidence. Burk's reassessment (1979a, b) reached the opposite conclusion, but used methods which are invalid. Burk's conclusion cannot therefore be sustained.

7.28 Similarly, Burk's analyses (1980, 1981) of the trends in cancer mortality in fluoridated Birmingham were inappropriate and misleading. They were based entirely on the mortality from cancers of all sites combined, and almost entirely on an examination of crude death rates. Burk's only attempt at standardisation for age was inadequate. Even his conclusion that an abrupt and sustained increase in crude rates occurred in Birmingham following fluoridation is untenable, depending as it did on an unacceptable selection of the data which most favoured his hypothesis, and on his failure to make appropriate comparisons with other areas. The almost instantaneous change in cancer rates which he associated with fluoridation is biologically implausible, and he provided no sound evidence of its existence.

7.29 In contrast, the careful analysis of the Birmingham data by Cook-Mozaffari et al (1981) standardised the cancer mortality rates for age and for each sex separately, matched the population and mortality data scrupulously, examined twelve individual sites of cancer in addition to all cancers combined, and considered long-term trends. Their analysis provided no evidence that fluoridation had affected cancer death rates.

CONCLUSION TO CHAPTER SEVEN

7.30 The examination of cancer rates for up to fourteen years after fluoridation in Birmingham, and up to eighteen years after fluoridation in Anglesey, and the investigation of cancer rates in areas with various levels of naturally occurring fluoride, provide substantial reassurance concerning the safety of fluoridation in respect of cancer. All statements to the contrary were based on errors.

CHAPTER 8

EPIDEMIOLOGY IN OTHER COUNTRIES

INTRODUCTION

8.1 The several papers which relate to countries other than the United States and the United Kingdom are briefly described here, in alphabetical order by country. The majority of authors found no association between fluoride in water and cancer. One of the five studies from Canada claimed that fluoridation increased cancer rates (Cecilioni, 1977). In contrast, the authors of a study from Norway speculated on a possible beneficial effect of naturally occurring fluoride (Glattre and Wiese, 1979).

AUSTRALIA

8.2 A Working Party of the National Health and Medical Research Council (1979) conducted a small time-trend study of cancer mortality in six Australian cities. The death rates for all cancers combined were standardised for age and sex by the direct method, using 10-year age-bands, and census years only. The standardised rates fluctuated considerably in the smaller cities. Comparison of the relatively stable rates in Sydney (fluoridated in 1968) and Melbourne (which did not fluoridate until 1977), for the census years 1961, 1966, 1971, 1976 showed very similar patterns of increase, but with a less rapid increase in Sydney.

8.3 Richards and Ford (1979) examined mortality rates for all cancers combined, in ten fluoridated and ten non-fluoridated localities in New South Wales. They calculated SMRs from annual average cancer deaths (in 5-year age-groups) for 1970-72. The average SMR for the fluoridated areas was below that for non-fluoridated areas; the range and distribution of SMRs in the two groups were similar. The authors concluded that "differences in cancer mortality in New South Wales (using standardised mortality ratios) are unrelated to whether a locality has a fluoridated water supply or not".

AUSTRIA

8.4 Binder (1977) reported a study of cancer deaths (aggregated over a twenty-year period) in relation to levels of naturally occurring fluoride in water. Nine 'high-fluoride' communities (1.0 ppm or more) were compared with ten 'reference' communities (0.2 ppm or less). In a series of comparisons, principally of those who had lived their whole lives in one community, Binder found that the number of cancer deaths, as a percentage of deaths from all causes, was no greater in the high-fluoride areas. However, nowhere in this study is an age-standardised rate given.

CANADA

8.5 An early study by Buck and Sellars (1960) was summarised briefly in the report of the Ontario Fluoridation Investigating Committee (Morden *et al.*, 1961). Age-standardised mortality rates were compared in eighteen pairs of 'fluoride' and 'non-fluoride' municipalities in Ontario, and for the three cities Brantford (fluoridated from 1945), Stratford (1-1.5 ppm fluoride naturally present in water) and Sarnia (with no fluoride in water supplies). The eighteen 'fluoride' municipalities were chosen to be those with a water

fluoride concentration of 1.0 ppm or greater and which could be paired with a nearby municipality of reasonably comparable size, having a water fluoride concentration of 0.4 ppm or less; the concentrations are presumably of naturally occurring fluoride. Cancer was one of the categories of disease studied. The authors concluded that "the mortality rates under consideration are not influenced by the fluoride concentration of the water supply".

8.6 Following the report of the Ontario Fluoridation Investigating Committee, many areas of Ontario have fluoridated their water supplies. Cecilioni (1977) reported several analyses of cancer death rates in 49 Ontario cities (26 fluoridated and 23 non-fluoridated). In each case the death rate was the crude death rate averaged over 9 years, (1966-74), as estimated from cancer deaths in the Vital Statistics for Ontario, and from the 1971 census figure for population. Cecilioni found higher rates in the fluoridated cities, as compared with the non-fluoridated cities, for several specific cancers, and all cancers combined. He concluded that "These comparisons . . . would tend to prove that there is a correlation, rather than a mere coincidence here". It was subsequently shown (McCullough, 1977) that the difference in crude cancer death rates between the fluoridated and non-fluoridated groups of the 49 cities was not statistically significant. Even if it were, it would not be possible to reach a reliable conclusion from an examination of crude rates alone.

8.7 Wigle et al., (1981) published a comparative study of cancer mortality data aggregated over the period 1966-76, for selected Canadian municipalities. Although the prime reason for the study was to investigate gastrointestinal cancers in relation to asbestos levels, correlations between age-standardised mortality rates and a number of aspects of water quality, including fluoridation, were assessed. Statistically significant positive correlations were found between fluoridation and mortality rates for four groups of cancers (gastrointestinal cancer in females, and cancers of colon with rectum, tongue with mouth and pharynx, and oesophagus in both sexes), but when adjustments for several socioeconomic and water quality characteristics were incorporated, these correlations disappeared or became negative. The authors commented that "given the limitations of this type of study, it seems pointless to speculate about the significance of identified associations unless they are consistent (e.g. present in both sexes) and confirmed in several independent studies".

8.8 In an unpublished comparison arising from the data collected during the above study, Wigle (personal communication) examined the average annual age-standardised mortality rates for 1966-76 at ages 25-69, for each sex. In a comparison between 34 fluoridated communities and 36 non-fluoridated communities, there were no cancer sites for which significantly high rates were observed in the fluoridated group. When these 70 communities, with 16 others, were grouped according to the period of initial fluoridation (1945-60, 1961-70, never), it was noted that the standardised mortality ratio was lowest in the group of those localities which had been fluoridated for the longest period. The rates for specific sites of cancer were similar in all three groups of localities, with no evidence of an adverse effect of fluoridation.

8.9 A report of the Department of National Health and Welfare of Canada (Raman et al., 1977) examined mortality from all cancers combined, and from several specific cancers, in 100 cities over the years 1954-73. Over half of the total population of Canada was included. The cities were combined according to the number of years of fluoridation (which ranged up to 28 years, in Brantford). The rates for each sex were standardised for age (by both direct

and indirect standardisation using 10-year age-groups). In a series of analyses, there were no consistent differences between cancer mortality rates in fluoridated and non-fluoridated communities, or between communities which had been fluoridated for different lengths of time, nor was there any association between fluoridation and the trends in cancer rates over time. The authors concluded that 'the absence of a consistent trend . . . lead(s) us to concur with the conclusion arrived at by the Royal College of Physicians that fluoridation does not increase the cancer risk of the population''.

ITALY

8.10 Mirisola and Cruciani (1964) compared four districts in Italy, with levels of naturally occurring fluoride in drinking water from 1 to 3 ppm, with three 'non-fluoride' districts. The index chosen for comparison was the average age at death from certain groups of disease, including cancer; the authors concluded that the average age at death, and frequency of the incidence of the individual groups of diseases, showed no differences in the 'fluoride' areas as compared with the 'non-fluoride' areas. The index chosen, however, can be a very misleading measure for such comparisons.

THE NETHERLANDS

8.11 Kinlen (1974, 1975) made a preliminary investigation of the crude incidence rates in 1966-69 for cancer of thyroid, kidney and bladder, in two cities in the Netherlands. The rate was lower in Rotterdam (100% fluoridated) than in the Hague (non-fluoridated). The analysis was taken no further.

NEW ZEALAND

8.12 Kinlen (1974, 1975) made a preliminary investigation of the crude incidence rates in 1965-9 for cancer of thyroid, kidney and bladder, in three areas of New Zealand. There was no appreciable tendency for the incidence of those cancers to be higher in fluoridated areas, but the influence of the age-structures of the populations was not taken into account.

8.13 Goodall *et al.*, (1980) examined cancer mortality for six areas of New Zealand which had been fluoridated by 1967, in a comparison with four non-fluoridated areas. They compared the census years of 1961 and 1976, using death rates for the over-45 population for each sex separately. The increase in crude rates from 1961 to 1976 was greater in the non-fluoridated areas. When rates specific for sex and age (ten-year age-bands) were examined, there were no statistically significant differences between fluoridated and non-fluoridated areas. The authors noted that there was ''no support for the assertion that fluoridation of public water supplies resulted in any increase in cancer mortality'', but ''some evidence that the rate of increase in cancer mortality over the 15 year period 1961-1976 had been greater in unfluoridated areas than that occurring in areas with fluoridated water supplies''.

NORWAY

8.14 Glattre and Wiese (1979) studied 121 municipalities with naturally occurring levels of fluoride up to 0.5 ppm (i.e. below the 1 ppm level recommended in fluoridation). They demonstrated, for both sexes, that the age-standardised mortality from oral and pharyngeal cancer decreased with increasing fluoride levels. They suggested that fluoride may exert a protective effect, but they pointed out that this relationship might be an artefact, or non-causal.

SOUTH AFRICA

8.15 The report of the South African Commission of Inquiry into Fluoridation (McKenzie *et al.*, 1966) contains the following statement: ''In

22 magisterial districts where the fluoride content of the water is more than 1.5 ppm the mortality rate for all cancers was 420.00 (expected 427.87) in females, and 474 (expected 503.47) in males. No increased trend in cancer incidence has been shown in this study''.

SWEDEN

8.16 Biörck *et al.*, (1965) in a study of correlations between water hardness and mortality from cardiovascular and other diseases, included measurements of the levels of naturally occurring fluoride (0.1-1.5 ppm), averaged over the years 1940-62. They estimated the average mortality rate for each disease for the years 1951-60, by broad age-groups and for each sex, in all 33 Swedish towns with more than 25,000 inhabitants. They did not report any significant correlations between fluoride level and mortality from any cancer, and none was apparent in their tables which refer to the age-group 45-64 only.

USSR

8.17 Knizhnikov (1959) compared the health of the populations of two similar cities in northern Kazakhstan. The fluoride level in the water of one city was 3.4-4 mg/l (from natural sources), while that in the other city was 0-0.9 mg/l (also from natural sources). The cancer mortality rate (apparently the crude death rate), for a period of five years, was lower in the city with the high level of fluoride. The analysis was taken no further.

DISCUSSION OF STUDIES CONSIDERED IN CHAPTER EIGHT

8.18 These studies display a wide variety of methods in their examinations of cancer rates in relation to the level of fluoride in water. The commonest fault among these papers from the epidemiological standpoint is a failure to allow for age differences in the populations under comparison; the sole claim of harm rested on an examination of crude rates only. Some of the reports do employ standardisation for age, but only in the Canadian studies by Wigle *et al.*, (1981) was standardisation for other factors, such as socioeconomic differences, incorporated. Areas which are contrasted for their fluoride values are described as comparable in other respects, but often without providing the evidence in support of that statement.

8.19 However, several of these papers are sufficiently thorough to allow interpretation. The Australian studies are well conducted, as are the report from the Canadian Department of National Health and Welfare, and the New Zealand study by Goodall and colleagues. All used age-standardised mortality rates and described clearly the areas which were under comparison. It is true that the time between the date of fluoridation and the assessment of mortality tended to be short in comparison with the usual long latency of cancer development, but there was no evidence of an adverse effect of fluoridation over the shorter periods studied (extending up to 28 years post-fluoridation in the Canadian report).

CONCLUSION TO CHAPTER EIGHT

8.20 Although the various studies described here have approached the subject of adverse effects of high fluoride concentrations from many different viewpoints, none of those which have an adequate epidemiological basis has found any evidence of harm from fluoridation.

CHAPTER 9

DISCUSSION AND CONCLUSIONS

QUESTIONS AND ANSWERS

9.1 In this chapter we must answer the fundamental scientific question of our enquiry: does fluoridation of drinking water cause cancer in men? In doing so, we must recognise that this question, although apparently simple, actually embraces several subsidiary considerations. First, either fluoride itself might be a cause of cancer (in which case cancer rates would be increased whether fluoride were naturally present in water or were added to reduce dental caries), or some other feature of fluoridation, perhaps a contaminant of the chemicals used, might be a cause. Second, the term 'cancer' includes not only all cancers taken together, but also specific cancers arising at individual sites in the body, or from different tissues, each of which might be studied separately. Third, not only must we consider effects upon the population as a whole, but also specific subgroups.

9.2 We must also address the complementary question of safety. Those responsible for public health work from the premise that even a procedure of proven benefit to human health should not be implemented on a wide scale until it has been shown, in practical terms, to be safe, that is that its benefits far outweigh any conceivable hazards. Even if we have been unable to find any evidence which suggests to us that fluoride causes cancer, we must still ask whether the safety of fluoridation of drinking water has been adequately tested in this respect. Since very small effects on health are difficult to detect and therefore to exclude, there can never be an assurance of absolute safety. The only practical approach for any suggested adverse effect is to ask whether the greatest effect which would be compatible with the evidence is so small as to be negligible.

9.3 The existing knowledge of the biology of cancer has a bearing both on our assessment of the epidemiological studies and on our answers to the questions above. We therefore comment first on the prior biological considerations. We next summarise what we have learnt from the three main types of studies of cancer rates in human populations in relation to fluoride levels in water. After considering the question of safety, we then set out our conclusions.

PRIOR BIOLOGICAL CONSIDERATIONS

9.4 It was not part of our task to review the biology of cancer induction. There is, however, extensive information on the origin and development of cancers in man and animals. Those aspects most relevant to our enquiry are considered briefly here.

Latency of Cancer

9.5 Cancer induction is a multistage process which encompasses a whole series of events stemming from the initial damage to the genetic material of the body's cells. Chemically-induced cancers usually develop slowly, and there is always a latent period between initial exposure to the chemical and the appearance of a tumour. This period will vary in any one species according to factors such as the type of chemical and the route of administration. As a rough guide, about 15 to 30 years may be cited for man. Even for radiation-induced cancers in children, which are exceptional for the rapidity of their development, the latent interval is rarely less than 3 years. Furthermore, after

the clinical detection of a cancer which proves ultimately to be fatal, there is usually a period of several years, and sometimes several decades, before death occurs.

9.6 The existence of the latent period between exposure to a chemical agent and the detection of cancer, and the delay between detection and death from a fatal cancer, has two implications for our present enquiry. First, long-term studies which have found no effect on cancer rates in populations exposed for many years must provide stronger reassurance of safety than short-term studies. Second, any epidemiological evidence which appeared to suggest that fluoridation affected cancer mortality rates immediately, or after a very few years, would need to be scrutinised with particular care and supported by other work before it could be accepted.

Specificity of Cancer Induction

9.7 Cancer-inducing chemicals do not act in a random fashion on all the tissues of the host. For each chemical, there are distinct 'target sites' which may be determined by such factors as the initial point of contact (skin, lungs, alimentary tract) or the sites where the chemical is metabolised (e.g. liver) or excreted (e.g. kidney, bladder). The target sites remain the same for a given species, and for a given route of administration. No individual chemical is known to cause a general increase in cancer incidence in man or animals.

9.8 In epidemiological studies, therefore, it is important to examine the rates for cancers of specific sites, or groups of sites. If different studies report an increase for all cancers taken together but are not consistent in terms of the sites affected, then it is most unlikely that any single chemical agent could be responsible for all of the increases in cancer rates. On the other hand, it must be recognised that the apparent absence of an effect on the combined rate for 'all cancers' could be misleading if there were a real effect on only one or a few specific cancers.

Variations in Susceptibility and Exposure

9.9 The response to a cancer-inducing chemical also depends on such characteristics of the exposed person as age, sex and ethnic group. Hormonal variations, for example, may modify the effect of a chemical on target tissues. Human beings have a capacity, albeit limited, to repair damaged genetic material, or to eliminate genetically-damaged cells. Where this capacity is deficient the result is an increased risk of developing cancer at various sites; this is most obvious in a few rare heritable abnormalities in man. Genetic strain (as well as species) is often important in determining cancer development in animals; in man, susceptibility to certain cancers varies between ethnic groups.

9.10 It is because of variations in susceptibility to cancer between different groups, but also because they are liable to vary in their exposure to agents which induce cancer, that demographic factors should be taken into account to the maximum extent possible in the design or analysis of epidemiological studies; where possible the results for the individual subgroups should be examined separately.

9.11 Age is the dominant influence on cancer rates. It is essential that age be taken into account in comparing cancer rates in different populations. Although the separate effects of sex and ethnic group are less marked for many cancers, the complex interaction of the three factors is often of great importance. Sex should always be included in the analysis, and where reliable data on ethnic group are available, it is generally appropriate to include that also.

EVIDENCE FROM THE EPIDEMIOLOGICAL STUDIES

Looking for the Causes of Cancer

9.12 Almost all of the published evidence relating to ingested fluoride and human cancer is based on the examination of cancer rates in populations whose exposure to fluoride has been gauged by the concentration of fluoride in drinking water supplies. This contrasts with the more specific estimates of individual exposure through which the causes of a wide range of individual cancers have been established. Examples are the effects of: tobacco smoke with respect to lung cancer; rubber antioxidants in relation to bladder cancer; ionising radiation in relation to some forms of acute leukaemia; asbestos inhalation in relation to mesothelioma and lung cancer; distilled alcoholic liquors in relation to cancers of the larynx and oesophagus; and hormone therapies in relation to cancers of the vagina and uterus. It is true that in some of these instances the initial clues were provided by studies in which individual exposure was not estimated, but the study of individuals has followed before a cause and effect relationship has been accepted. Lung cancer rates, for example, were initially associated with population exposures to tobacco; this led to investigations showing that in general individuals with lung cancer had previously smoked more than individuals without lung cancer. Later still, individuals who admitted to smoking were shown to have a higher risk of subsequent development of lung cancer than those who had not smoked. Consistent quantitative relationships were demonstrated between the amount smoked and the level of increased risk.

9.13 Our purpose in considering these examples is to emphasise that, while epidemiological techniques for detecting the causes of cancer are well developed, and have proved themselves in practice, evidence based solely on the statistics of aggregated communities needs special care in its interpretation. In relation to the question before us, however, there are particular advantages inherent in the ability to select communities whose entire water supply is fluoridated, or not fluoridated. Exposure to fluoride in water is more nearly uniform within such communities than would be the case with most other environmental factors which might be examined. It is therefore unlikely, if there were in fact a genuine effect of fluoridation on cancer, that it could be missed.

9.14 The only study in which exposure to a source of fluoride has been assessed in individuals found that different levels of intake of tea, which is the major source of dietary fluoride in the United Kingdom, had no effect on the incidence of cancers of stomach, breast, lung or intestine, or on the combined incidence of the other cancers (Stocks, 1958).

9.15 The many other studies of cancer rates have classified communities according to:

(i) the concentration of fluoride naturally present in drinking water, or

ii) the presence or absence of artificial fluoridation of water supplies. Studies in the second group can be subdivided into those which have compared:

(a) cancer rates for a single period, or

(b) trends in cancer rates over a period.

In the body of the report, we have discussed all these studies, often in considerable detail, according to a geographical classification, and with emphasis on those studies on which the claim of an effect of fluoridation has been largely based. Here, in the next three subsections, we briefly review the outcome of the epidemiological studies according to the more meaningful classification outlined above.

Comparisons in areas with differing natural levels of fluoride

9.16 The particular value of studies of populations exposed to differing natural levels of fluoride in the drinking water is that individual exposure will often have been long-term. The uncertain length of the latent interval between exposure to a chemical and the appearance of cancer is not an important complication in the interpretation of such studies. The only factor likely to upset their reliability in this respect would be large-scale emigration from or immigration to the communities involved.

9.17 If there were a relationship between fluoride in water and cancer, it should therefore be detectable in studies of this kind, given a sufficiently large set of data. We are aware of twenty papers which examined cancer incidence or mortality, for all cancers combined, or for separate sites of cancer, in relation to natural levels of fluoride. Every investigator concluded that there was no adverse effect of fluoride.

9.18 The largest group of such studies concerns American data (see Chapter 6, para 6.2 onwards). Studies by Hagan *et al.*, (1954) of 32 cities, and Hoover *et al.*, (1976) of 53 Texas counties, both examined the mortality for all cancers combined, in relation to a wide range of fluoride levels. Hoover and his colleagues also considered thirty-four separate sites of cancer in a very thorough analysis, the results of which provided no evidence of any effect of fluoride on cancer. The study by Austin (1975) of 50 counties reached the same conclusion for seven sites of cancer.

9.19 Four published analyses of data from the United Kingdom were available to us (see Chapter 7, para 7.2 onwards). That by Weaver (1944) only considered crude (uncorrected) mortality rates for all cancers combined, but Heasman and Martin (1962) standardised the mortality rates for age and sex. The only finding from their study which could be thought to be a matter for concern was a localised excess of stomach cancer for the 'high-fluoride' towns of northern England. The finding was not reflected in any parallel finding in either sex for the compared towns of southern England, and has not been repeated in any subsequent study of stomach cancer and naturally occurring fluoride. These later studies, including an extended analysis of cancer mortality in the same areas (Nixon and Carpenter, 1974), have confirmed the conclusion that "the difference in fluoride levels is most unlikely to have been the cause of the difference in mortality" (Heasman and Martin, 1962).

9.20 The incidence of cancer of nine selected sites was studied in 96 areas of the United Kingdom by Kinlen (1974, 1975). No effect of fluoride was detected. We have ourselves extended Kinlen's study by incorporating more detailed information on water fluoride levels, data for more recent years, and additional sites of cancer. We have also analysed the mortality data. Nowhere in these analyses of cancer incidence or mortality, for any specific site of cancer or for all cancers combined, has there been any evidence of a harmful effect of fluoride (Chilvers and Conway, 1985; see also Appendix 3).

9.21 None of the studies carried out in Austria (Binder, 1977), Canada (Buck and Sellers, 1960), Italy (Mirisola and Cruciani, 1964), Norway (Glattre and Wiese, 1979), South Africa (McKenzie *et al.*, 1966), Sweden (Biörck *et al.*, 1965) and the USSR (Knizhnikov, 1959) suggested a harmful effect of fluoride, and indeed the authors of the Norwegian study went so far as to speculate about a possible beneficial effect on oral and pharyngeal cancer. It is more likely, however, that there is no effect at all.

9.22 These investigations in the United States, United Kingdom and seven other countries relate in the main to long-term or even life-time exposures to fluoride levels which span and exceed the range appropriate to decisions concerning artificial fluoridation. Taken together, they are based on very large numbers. The absence of a detectable harmful effect of fluoride on cancer as a whole, or for cancer of any individual sites, provides a high level of reassurance concerning safety.

Comparisons of cancer rates for a single period in fluoridated and non-fluoridated areas

9.23 In contrast to the unanimous conclusion of the authors of the above studies that there was no evidence that fluoride present naturally in water was a cause of cancer, investigations based on artifical fluoridation have reached contradictory conclusions. There has been total polarisation between the conclusions of one pair of workers (Yiamouyiannis and Burk) and those of almost all others. From their comparisons of cancer rates between areas with or without artificial fluoridation, Yiamouyiannis and Burk concluded that the addition of fluoride to water supplies caused an increase in mortality from cancer, while the other investigators did not find evidence of the existence of any such effect.

9.24 Yiamouyiannis and Burk first reached their conclusion on the basis of simple comparisons of certain United States cancer rates for one particular period (Yiamouyiannis, 1975a, 1975b, 1975d; Burk and Yiamouyiannis 1975; Yiamouyiannis and Burk, 1977). These studies are considered in detail in Chapter 3. All are seriously flawed by a failure to consider whether the areas being compared were sufficiently similar with respect to factors other than fluoridation, and by one or more defects of technique, including the use of cancer rates of uncertain relevance to the communities under study, the exclusion of data which did not agree with the hypothesis of harm from fluoridation, the use of incorrect methods for combining data, and the unjustifiable extrapolation to whole population of results based on only one group within the population.

9.25 The data used by these authors on the mortality from nine specific cancers (Yiamouyiannis, 1975d; Burk and Yiamouyiannis, 1975) were reanalysed by Hoover *et al.*, (1976). The reanalysis demonstrated that the differences in cancer mortality rates were essentially due to differences between the populations other than fluoridation status. When appropriate corrections were made there were no remaining statistically significant associations consistent (where applicable) in both sexes. The only statistically significant association, for stomach cancer in males only, was not confirmed in any other investigations of artificial fluoridation.

9.26 Three other such studies of American data (Austin, 1975; Erickson, 1978; Neuberger, 1982) have not detected any harmful effect of fluoridation on the incidence of or mortality from cancer of any site, including stomach cancer. The study of Erickson, which included areas with high natural levels of fluoride in the fluoridated group, is of particular interest in that it considered mortality from a wide range of diseases in addition to cancer. The crude mortality rates for most of the diseases were greater in the fluoridated group but, when demographic and socioeconomic factors were taken into account, there was little difference between the mortality rates, for any of the diseases, in fluoridated and non-fluoridated cities.

9.27 The importance of suitable correction of crude rates is obvious from Erickson's study, and is also apparent when we turn to the Canadian data. The only study which has reached the same conclusion as Yiamouyiannis and

Burk is an examination of crude mortality rates in Canadian cities (Cecilioni, 1977). More careful Canadian studies, however, have found no evidence that fluoridation affects cancer rates (Wigle, 1981; Wigle, personal communication) or the trends in cancer rates (Raman *et al.*, 1977).

9.28 In the United Kingdom, Kinlen (1974, 1975) studied the incidence of several cancers in fluoridated and non-fluoridated areas, and reported that there was no evidence of harm from fluoridation. Burk (1979a, b) reworked Kinlen's data and reached the opposite conclusion, but his analysis relied on special selections from the data. We are in no doubt that Burk's inappropriate method led him to a false conclusion.

9.29 A study in Australia (Richards and Ford, 1979), using well-validated methods of analysis, concluded that differences in cancer mortality in New South Wales were not related to the presence or absence of a fluoridated water supply.

9.30 We are clear that the conclusions of Yiamouyiannis, Burk and Cecilioni were based on the inappropriate use of data and faulty analyses; their conclusions were not supported by the results of a number of other simple comparisons of cancer rates in fluoridated and non-fluoridated communities in which normal analytical methods were used. These studies provide no evidence that fluoridation alters cancer rates.

Studies of trends in cancer rates in relation to fluoridation of water

9.31 Over thirty studies have compared the changes in cancer rates with time, in fluoridated and non-fluoridated areas. If fluoridation increases cancer rates in the short term, then such studies should show a greater increase of cancer rates in areas which have been fluoridated. Again, there has been total polarisation between Yiamouyiannis and Burk and almost all other workers.

9.32 The principal basis for the conclusion of Yiamouyiannis and Burk that fluoridation causes cancer is to be found in their series of analyses of cancer mortality rates in two groups of cities in the United States. We have discussed these analyses in detail in Chapter 4. We have found that none of them is technically satisfactory. Like the earlier simple comparisons of cancer rates by the same authors, their time-trend studies are seriously flawed. One of the major defects has been their persistent failure to take properly into account the effects of age, sex and ethnic group by using routine and well validated methods for the correction of crude mortality rates.

9.33 Even where Yiamouyiannis and Burk have attempted to correct the crude mortality rates, they have preferred untried methods of their own design to widely used and validated standard techniques, and have failed to question whether their unusual methods may be responsible for their unusual results; in particular, they chose to use the unreliable figures for years remote from census years in order to extrapolate forward beyond their data, preferring the resulting estimates of death rates to those derived from the sound and relevant data which are available for census years. They have often neglected the crucial importance of the natural variability of cancer rates between populations; where they have calculated the statistical significance of their results, the tests used have been inappropriate and the conclusions erroneous.

9.34 Several other groups have examined the trends in cancer mortality in the cities chosen by Yiamouyiannis and Burk. These studies are summarised

in Chapter 5. On the basis of generally accepted methods of analysis, all have concluded that there is no evidence of a harmful effect of fluoridation. Our own analyses confirm the absence of a demonstrable effect on the mortality either for all cancers combined or for cancer of any specific site (Chilvers, 1982; Chilvers, 1983).

9.35 Yiamouyiannis has criticised a number of technical aspects of the reanalyses by other authors. Such matters as the relative merits of two alternative types of standardisation, the choice of reference population (or reference rates), weighted and unweighted averages, and the inclusion or otherwise of cities which had been fluoridated for only a few months, have been the subject of extended discussion. In our own analyses, as in those of other authors (e.g. Kinlen and Doll, 1981), these matters turn out to be of little consequence; the conclusions are unaltered. The arguments surrounding these particular aspects of technique have merely diverted attention from the major deficiencies in the studies by Yiamouyiannis and Burk, and have obscured the considerable weight of evidence which refutes their conclusions.

9.36 Several studies of United States data, including our own, included cities additional to those chosen by Yiamouyiannis and Burk (Taves, 1979; Kinlen and Doll, 1981; Chilvers, 1983). Other authors examined cancer rates in far more extensive populations in the United States (Hoover et al., 1976; Rogot et al., 1978). Hoover and his colleagues considered not only the mortality rates for all cancers combined, but also those for a comprehensive range of sites of cancer. They were also able to conduct a more limited study of cancer incidence. No harmful effect of fluoridation was detected in any of these investigations.

9.37 In the United Kingdom, the main object of study has been cancer mortality in Birmingham, which, with some other parts of the West Midlands conurbation, has been fluoridated since 1964. Burk (1980, 1981), following leads by Brady (1977) and Schatz and Schatz (1972), claimed that the crude death rate for all cancers combined had risen excessively only one or two years after fluoridation had begun, and that the increase was linked to fluoridation.

9.38 In view of the latency of induction of cancer, and the time between detection of cancer and death from this cause, it would be extremely surprising if Burk's interpretation were correct. Cook-Mozaffari and Doll (1981) have shown that in fact the changes in crude mortality rate in Birmingham throughout the period 1951-1978 were similar to those in non-fluoridated English cities over the same period, and therefore that the basis for Burk's conclusion was false.

9.39 Much more important than these examinations of crude rates were the several analyses of age-standardised rates in Birmingham (Kinlen et al., 1980; Cook-Mozaffari and Doll, 1981; Cook-Mozaffari et al., 1981). The comparisons with non-fluoridated conurbations showed no adverse effect of fluoridation on mortality from cancer in general, or for specific sites of cancer.

9.40 Our consideration of the investigations by Yiamouyiannis and Burk of the trends in cancer mortality in fluoridated areas in the United States and the United Kingdom, our studies of the reanalyses of those trends by other workers, and our own reanalyses and reassessments, leave us in no doubt that

Yiamouyiannis's and Burk's conclusions of a harmful effect of fluoridation on cancer were unsoundly based. The correct interpretation of the data leads to the conclusion which has also been reached in all other studies of cancer trends in the United States, the United Kingdom, Canada, Australia and New Zealand. There is no evidence from these studies to suggest that fluoridation affects cancer.

THE QUESTION OF SAFETY

9.41 We conclude that there is no substantiated evidence from studies of human populations that fluoride or fluoridation causes cancer, or increases mortality from cancer, whether for cancer as a whole or for cancer at individual sites. The notion that fluoridation and cancer were associated seems to have arisen as a result of the fact that, amongst the major cities of the United States, fluoridation was introduced earliest in those which were relatively disadvantaged in social and economic terms (as can be seen by the effects of the corrections for such factors in the paper of Erickson, 1978), which already had relatively high standardised cancer rates (Oldham and Newell, 1977) and which, because the proportion of the elderly was increasing particularly fast, had crude rates which were increasing particularly fast. Each of the epidemiological studies whose authors have concluded or implied that fluoridation causes cancer has been shown to be unsoundly based. The conclusions of those studies arose from elementary errors, most importantly a failure to use standard and well tried approaches which would allow properly for these important demographic and socioeconomic differences between populations. In addition these authors employed many inappropriate unvalidated methods; many of the types of error which we have described in Chapter 1 played a part in the false conclusions reached by Yiamouyiannis, Burk, Brady, Schatz and Schatz, and Cecilioni. Each of these authors has failed to ask the fundamental question proposed by Bradford Hill (1977): ''Is there any other answer which is more likely than cause and effect?''. Their repeated analyses, principally of just two basic sets of data, but with a variety of method and argument, may have given the impression of a complex body of evidence; on examination, however, each strand of that evidence is unsound and the conclusions drawn from it by the authors can be unreservedly dismissed. It has been left to other authors' studies of cancer rates in the same populations, and often of the same data, to show that there is in fact no evidence of an adverse effect when well-established and sound methods of analysis are used

9.42 We turn therefore to our second question: Can we say that fluoridation is safe? We note first that the numbers involved in the many investigations which we have reported are probably greater than those marshalled in relation to any other public health procedure. The investigations cover hundreds of communities, corresponding to many millions of people and tens of thousands of cancer deaths and cancer cases arising in the normal course of events. The matter has been put to the test in a variety of circumstances, and a range of different outcomes has been measured, including both mortality and incidence for cancer as a whole and for cancer at different sites. The findings cover each sex, a range of age-bands, and different ethnic groups. The consistency of the results and conclusions, apart from those clearly attributable to errors of analysis, provides powerful reassurance of safety. Indeed the standardised cancer rates have tended to be lower in the fluoridated areas, and in the areas with high natural levels of fluoride, than in the areas with little or no fluoride in the drinking water. Although this is certainly not evidence that fluoride actually protects from cancer, it adds to the confidence with which it is possible to assert the safety of fluoridation.

9.43 We have carefully considered whether any reservations should be entered regarding the strength of this reassurance. One important question arises from our expectation of a lengthy latent interval for cancer induction. The short-term time-trend studies effectively excluded an almost immediate effect, but they are as incapable of demonstrating long-term safety as they are of demonstrating any increase in cancer arising after a latent period of several decades. Only two published studies (Raman *et al.*, 1977; Rogot *et al.*, 1978) have included a few populations who have been using artificially fluoridated drinking water for over twenty years; they have not shown any effect on cancer rates. Many of the remaining studies relate to exposure of fifteen to twenty years, but this is on the short side for complete reassurance. We therefore attach special importance to the extensive studies of cancer rates in relation to various levels of fluoride naturally present in water, with lifetime exposure for much of the population. Here we have a method which should reveal a cancer-inducing effect if it existed; none has been demonstrated. It is desirable, nevertheless, that cancer rates should continue to be examined in fluoridated areas; even though there is no reason to anticipate that fluoridation will influence cancer rates, such surveillance should, out of prudence, be a routine.

9.44 It has sometimes been suggested that artificial fluoridation presents a cancer risk through some mechanism other than the action of fluoride itself; that is, that there could be an impurity present, or that the specific chemicals used for fluoridation could themselves produce cancer. This would divorce the strong reassurance obtained from studies of natural levels of fluoride from the question of the safety of the public health measure. However, nowhere have we seen any other allegedly cancer-inducing factor specified, nor are we aware of any other aspect of the process of fluoridation which could reasonably be implicated.

9.45 A further question which we have considered in relation to safety is whether evidence relating to every specific site of cancer, or to every specific subgroup of the population, has been sufficiently examined. In fact, quite extensive information on cancer rates by site is available, and no association between fluoride or fluoridation and cancer at any site or group of sites has been detected. Occasional high or low rates have been reported for individual sites in particular studies, but have never been confirmed on looking at the full range of available information; that is to say, no consistent association of any kind, at any site, or in any subgroup of the population, has emerged from the evidence.

CONCLUSIONS

9.46 We have found nothing in any of the major classes of epidemiological evidence which could lead us to conclude that either fluoride occurring naturally in water, or fluoride added to water supplies, is capable of inducing cancer, or of increasing the mortality from cancer. This statement applies both to cancer as a whole, and to cancer at a large number of specific sites. In this we concur with the great majority of scientific investigators and commentators in this field. The only contrary conclusions are in our view attributable to errors in data, errors in analytical technique, and errors in scientific logic.

9.47 The evidence permits us to comment positively on the safety of fluoridated water in this respect. The absence of demonstrable effects on cancer rates in the face of long-term exposures to naturally elevated levels of fluoride in water: the absence of any demonstrable effect on cancer rates

following the artificial fluoridation of water supplies: the large human populations observed: the consistency of the findings from many different sources of data in many different countries: lead us to conclude that in this respect the fluoridation of drinking water is safe.

9.48 The routine monitoring of public health has been an important feature of many fluoridation programmes, and has contributed to the confidence with which we can assert the safety of fluoridation with respect to cancer. We recommend that such monitoring should continue.

STANDARDISATION

Crude Rates and Standardised Rates

The crude rates of cancer incidence and mortality in a human population depend on a large number of characteristics of the population. The influence of three of these characteristics (the age-distribution, proportions of males and females, and the racial composition of the population) has been studied extensively.

The age-distribution of a population is by far the most important of the three demographic characteristics in this respect. In general, cancer mortality is much greater in older people than in younger people, as may be seen from Table A1.

Table A1: Death rates for malignant neoplasms by age, race and sex: USA, 1950 Rates per 100,000 population   (Oldham and Newell, 1977)

Age Group	White Males	White Females	Non-White Males	Non-White Females
0 −	12.4	10.6	8.6	7.1
5 −	7.6	6.3	5.7	4.0
15 −	9.9	7.5	7.7	8.6
25 −	17.7	20.9	17.9	33.5
35 −	44.5	74.5	56.0	119.3
45 −	150.8	185.8	207.4	273.3
55 −	409.4	362.5	484.8	481.0
65 −	798.7	616.5	632.7	476.9
75 −	1,367.6	1,026.6	844.4	578.9
85 +	1,732.7	1,348.3	916.0	716.0

Therefore a population which contains a high proportion of old people will have a greater crude cancer death rate than a population which contains a lower proportion of old people, but which is equivalent in other respects.

It is obvious that the two sexes will have different rates of cancer for their respective genital organs, and also for organs associated with secondary sexual features (e.g. breast), but the rates of cancer of other organs (e.g. bronchus) are also different. There are also differences in the mortality from all cancers together; in the older age groups, for example, the mortality rate is higher in men than women. However the effect of sex on the mortality from all cancers combined is much less marked than the effect of age.

Racial differences in cancer rates may also be important, although again the effect is less marked than that of age. The three factors of age, sex and race interact in a complex fashion (Table A1: these data are the basis for Fig 2 in the main text).

Other characteristics of the population may also influence cancer mortality rates; stomach cancer, for instance, tends to be commoner in the lower social class groups. If, then, the cancer rates in populations are compared in an exploration of a possible relationship between cancer and another factor (in the present context, fluoridation), it is essential that every effort should be made to allow for the effects of all the other relevant characteristics of the populations concerned before any conclusions are drawn. In practice, it is not possible to be comprehensive, and it may only be practicable to allow for age and sex, and, in the United States, for ethnic group. If no account of *any* of

these is taken, and therefore only crude rates are used, the results are likely to be most misleading, and the wrong conclusions may be reached.

The only fully satisfactory way to compare the cancer rates in populations is to consider the rates in comparable narrow groups. An example of such a group would be white males aged 40 to 44 years inclusive. It is often helpful, however, to derive a single summary mortality-rate for each population to replace the crude death rate, thereby facilitating comparisons between whole populations. This is achieved by the technique of standardisation, of which there are two commonly-used types: 'direct' and 'indirect'. The choice of the type of standardisation usually depends on the degree of detail available in the data, direct standardisation demanding greater detail. Both types of standardisation require additionally the nomination of a 'standard' or 'reference' population.

The two types of standardisation are outlined below. For simplicity, only adjustment for age is described, but the extension of the technique to include sex and race is straightforward. Similarly, although cancer mortality is considered here, cancer incidence may be analysed in the same way.

Direct Standardisation   To use this method, it is necessary to know:

> i. the mortality rates in each of the populations under study, in suitably narrow age-bands (for example, the rate for 15-19 year olds, 20-24 year olds, 25-29 year olds, and so on). This requires that for each age-band the number of deaths and the number of individuals are known.

> ii. the number of individuals in each age-band in the 'standard' population. The standard population may be any population with a structure which is reasonably similar to the structure of the populations under study, and whose age-distribution is known reliably.

Then each age-specific mortality rate from i. is multiplied by the number of individuals in the appropriate age-band in the standard population, the result being a 'number of deaths' for each age-band. These numbers are added, and the total 'number of deaths' is divided by the total number of individuals in the standard population. The result is the directly age-standardised cancer death rate. This can be compared with the age-standardised rates obtained from other populations by the same process.

Indirect Standardisation   Often only the *total* number of deaths in the population under study is known, making direct standardisation impossible. It is usually easy, however, to find a standard population for which the number of deaths and the number of individuals are known accurately for narrow age-bands. Indirect standardisation may then be applied. It is necessary to know:

> i. the number of individuals in each age-band in the population under study, and the total number of deaths in the population (this is called the 'observed number of deaths');

> ii. the mortality-rates of the standard population, in each appropriate age-band.

Then each age-specific mortality rate from ii. is multiplied by the number of individuals in the appropriate age-band in the study population, the result being a 'number of deaths' for each age-band. These numbers are added to produce the 'expected number of deaths' for each age-band. These numbers are added to produce the 'expected number of deaths' in the study population. The observed number of deaths is then divided by the expected number, the

STATISTICAL SIGNIFICANCE

The purpose of a test of statistical significance is to facilitate the assessment of the strength of evidence from a body of data for a genuine association between two factors (e.g. cancer death rate and the fluoride content of water supplies).

If there were no association between cancer rates and fluoride, we would expect the average cancer death rate for a group of fluoridated communities to be the same as the average cancer death rate for a group of non-fluoridated communities, all else being equal. Cancer death rates are subject to chance variations, however, and it may be that an observed difference between the death rates for the two populations has arisen as a result of such variation, and not from any effect of fluoride. Given an observed difference between rates, statistical theory enables us to calculate the probability that a difference at least as large could have arisen by chance.

This probability, commonly called a P-value, lies between 0 and 1. If the probability P is small (e.g. less than 0.05), we prefer the explanation that the difference has *not* arisen by chance, but has some other cause — that is, the observed difference in death rates is said to be 'statistically significant'.

Caution is necessary, however, in the interpretation of a 'statistically significant' difference, particularly when it arises in one of a large number of comparisons. To see this, consider a study of two populations in which the differences in death rates for sixty disease categories have been computed. When P is quoted as 0.05 for a given difference in rates, the interpretation is that a difference of at least this magnitude would be expected to occur by chance in one out of every twenty comparisons, in the *absence* of any factor systematically affecting death rates in one population more than in the other. Thus, of the sixty computed differences in death rates, three would be expected to be 'statistically significant at the 0.05 level' by chance alone.

The statistical test enables the evidence from a study to be weighed against the uncertainties arising from sources of variation beyond the control of the observer. Clearly, systematic influences, such as age in the studies of cancer rates, should be taken into account before significance tests are undertaken.

The concept of statistical significance is separate from the notion of 'cause and effect'. Whether or not a difference or an association that has been shown to be statistically significant can be regarded as evidence of cause and effect depends on a careful interpretation of the results in the light of the outcome of other relevant studies, and of basic biological knowledge.

Statistical significance and biological importance are also quite distinct. It is possible for a result to be statistically significant but of negligible biological consequence. Conversely, it is possible for a study to reveal an effect that would be large enough to be of biological importance but which fails to be statistically significant, perhaps because of inadequate study design.

Several different tests of statistical significance are available, each appropriate to particular circumstances. Incorrect conclusions may result if

result being the Standardised Mortality Ratio (SMR). Sometimes the SMR is multiplied by 100, by convention. If the population under study were identical to the standard population, in all characteristics except age-structure, the SMR would be 1 (or 100, in the alternative form). The SMR may be converted into an indirectly standardised rate by multiplying it by the crude rate for the standard population.

The Choice of Standard Population

If a population which differs markedly from the studied populations in structure is chosen as the standard population, standardisation of either type may produce misleading results. Subject to that proviso, any population whose structure is reasonably similar to those of the populations under study, and for which the requisite data are known reliably, is acceptable. Often the whole population of the relevant country in a suitable census year is chosen; alternatively, it is sometimes possible to pool the various populations under study. Irrespective of which choice is made, only one standard population should be used in each set of comparisons of study populations. If more than one standard population is used, the standardised rates will themselves be affected by differences between the standard populations, which are not the subject of the study.

The Choice of Method of Standardisation

In general, the choice of the type of standardisation used depends on the degree of detail in the data for the population(s) under study. Direct standardisation cannot be applied if the number of deaths in each age-band is unknown; when it can be applied, it may be misleading if the populations at the different ages are small, so that the death *rates* are subject to relatively large error. Both types of standardisation however, are perfectly acceptable in most circumstances. Both procedures have the advantage that the mortalities of populations are expressed as single numbers which can be compared readily; both have the disadvantage that no summary number can contain all the information in the detailed data.

inappropriate tests of significance are used. We have encountered examples, in the studies which we have reviewed, of incorrect conclusions arising in this manner. We have also encountered examples of incorrect conclusions arising from the failure to conduct significance tests.

Table A2: Results of Naturally-occurring fluoride — Incidence Study
1969-1973 SRRs (No. of cases)

		High	Low	Medium	Very Low
All cancers	M	*96.00 (3073)	108.78 (3220)	*96.67 (3474)	102.45 (3560)
	F	*95.33 (3011)	109.74 (3298)	98.98 (3378)	99.65 (3436)
Buccal cavity	M	87.08 (72)	116.69 (90)	110.67 (104)	89.44 (81)
and pharynx	F	106.08 (45)	113.50 (46)	97.85 (45)	88.10 (41)
Oesophagus	M	95.24 (63)	107.49 (65)	*76.12 (56)	116.25 (83)
	F	*69.13 (37)	113.18 (56)	109.11 (60)	113.90 (65)
Stomach	M	102.55 (249)	102.57 (226)	93.69 (251)	107.97 (281)
	F	*94.16 (155)	119.35 (181)	*86.90 (146)	110.57 (194)
Intestine	M	90.69 (181)	110.38 (201)	*84.34 (187)	110.72 (238)
	F	*88.20 (240)	112.38 (285)	91.56 (259)	105.57 (309)
Rectum	M	*85.17 (153)	118.55 (193)	98.44 (195)	102.47 (197)
	F	107.18 (144)	111.92 (139)	90.30 (125)	92.17 (132)
Pancreas	M	94.65 (86)	97.99 (81)	103.32 (104)	106.54 (104)
	F	97.33 (81)	104.47 (80)	97.62 (83)	102.67 (91)
Lung	M	*91.67 (784)	111.93 (884)	*93.93 (898)	109.24 (1013)
	F	96.97 (193)	109.02 (204)	96.69 (204)	98.76 (212)
Melanoma	M	*50.16 (8)	122.77 (20)	112.94 (22)	103.20 (19)
	F	*49.97 (17)	152.27 (52)	103.12 (41)	87.83 (34)
Other skin	M	113.90 (385)	103.00 (326)	*108.20 (416)	80.49 (299)
	F	113.00 (324)	106.15 (285)	*106.53 (320)	80.01 (248)
Bladder	M	113.68 (268)	100.23 (215)	89.66 (234)	106.64 (270)
	F	106.54 (80)	111.81 (83)	83.58 (65)	102.89 (83)
Kidney	M	103.23 (47)	98.87 (43)	96.37 (51)	108.50 (55)
	F	105.46 (34)	112.69 (34)	107.46 (37)	98.32 (34)
Other urinary	M	101.75 (47)	99.80 (44)	96.94 (52)	108.97 (56)
	F	111.67 (38)	113.07 (36)	102.01 (37)	98.68 (36)
Breast	F	93.84 (705)	102.42 (742)	103.28 (857)	101.17 (840)
Ovary	F	100.15 (154)	114.97 (170)	96.22 (163)	90.40 (153)
Thyroid	M	118.87 (8)	93.46 (6)	140.13 (11)	67.20 (5)
	F	68.10 (13)	107.76 (20)	104.12 (22)	122.87 (26)
Bone	M	129.59 (12)	95.85 (9)	92.17 (10)	105.16 (11)
	F	108.19 (7)	124.42 (8)	53.26 (4)	151.10 (11)

*P<0.05

102

CANCER INCIDENCE IN ENGLAND IN RELATION TO LEVELS OF NATURALLY- OCCURRING FLUORIDE IN WATER SUPPLIES

This appendix gives the detailed results of the study of cancer incidence in England, commissioned by the Working Party. The study is discussed in Chapter 7 of the report (paras 7.8-7.9).

Areas used for study

Naturally-occurring fluoride was classified as follows:

'High'	1.0 ppm or more.
'Medium'	0.5-0.99 ppm.
'Low'	0.2 ppm or less.
'Very Low'	0.1 ppm or less.

As a starting point the areas used by Kinlen (1974) were investigated. Fluoride levels were checked against data (obtained from the water authorities) which had not previously been available. Where more than one source supplied a local authority area, a weighted mean was calculated. On this basis, some areas were found to have been misclassified and had to be excluded, but it was possible to find a few additional areas. As in Kinlen's study, each 'high' area was matched with a 'low' area, and each 'medium' area with a 'very low' area. Matching was carried out on the basis of urban/rural status, and (as far as possible) for population size and geographical proximity. (Chilvers and Conway, 1985).

Incidence data

Numbers of new registrations of cancer occurring in each area were supplied by the Office of Population Censuses and Surveys for each year from 1969 to 1973. These were broken down by sex and age-group (0-4, 5-14, 15-24 . . . 75-84, 85+). Age-specific incidence rates for each cancer site were calculated for the aggregate of the 67 areas, using the 1971 census populations in the corresponding age-groups summed over all 67 areas as denominators. These incidence rates were used for the indirect standardisation, the rates being applied to the age-sex-specific populations of each area to calculate expected incidence. The observed and expected number of cases were each summed in each of the four fluoride groups and a Standardised Registration Ratio (SRR) calculated for each group of areas. This was carried out for 14 sites of cancer for men and 16 sites for women.

In view of the matching of areas, only comparisons of 'high' with 'low' areas, and 'medium' with 'very low' areas, are valid for each cause of death. A conventional text of significance based on the normal distribution was used.

REVIEWS BY OR FOR OFFICIAL BODIES

Australia

Crisp M P (1968) Report of the Royal Commissioner into the Fluoridation of Public Water Supplies. Tasmania. Hobart.

Howells G (1979) Annual Report of the Director General of Health, 1978-79. Canberra.

National Health and Medical Research Council, Australia (1979)
Submission to Committee of Inquiry into the fluoridation of Victorian Water Supplies.

Myers D M, Plueckhähn V D and Rees A L G (1980)
Report of the Committee of Inquiry into the Fluoridation of Victorian Water Supplies for 1979-80. Melbourne.

Canada

Morden K G, Hall G E and Frankel E L (1961)
Report of the Committee appointed to Inquire into and Report upon the Fluoridation of Municipal Water Supplies. Ontario.

Rose D and Marier J R (1977)
Environmental Fluoride, 1977. National Research Council, Canada.

Canadian Public Health Association (1979)
Criteria Document in Support of a Drinking Water Standard for Fluoride. Ottawa.

Canadian Dental Association (1981)
Water Fluoridation in Canada — a Status Report. CDA Journal 1981, Supplement.

New Zealand

Stillwell W F, Edson N L and Stainton P V E (1957)
Report of the Commission of Inquiry on the Fluoridation of Public Water Supplies. Wellington.

Norway

The Committee on Fluoridation (1968)
Report dated October 4, 1968. Oslo.

South Africa

McKenzie, W J, Becker B J P, Dreyer C J, du Toit J, Dowdle, E B D and deGraad, J W (1966)
Report of the Commission of Inquiry into Fluoridation. The Government Printer, Pretoria.

Sweden

Department of Social Affairs (1981)
Report of the Fluoride Commission. Stockholm.

United Kingdom

Ministry of Health, Scottish Office, Ministry of Housing and Local Government (1962)
The Conduct of the Fluoridation Studies in the United Kingdom and the Results Achieved after Five Years. Reports on Public Health and Medical Subjects No. 105. HMSO London.

Royal College of Physicians (1976)
                    Fluoride, Teeth and Health. Pitmans, London.

United States

National Academy of Sciences (1977)
                    Drinking Water and Health. Washington.
Anders M W, Dorsen P and Steenson M K (1979)
                    Report on the Governor's Commission on Fluoridation. Minnesota.
Department of Health and Human Services (1981)
                    Summary of Studies and Evaluations since 1976. Atlanta, Georgia.

World Health Organisation

Expert Committee on Water Fluoridation (1958)
                    First Report. Technical Report Series No. 146. Geneva.
International Agency for Research on Cancer (1982)
                    IARC Monograph, Vol. 27. Lyon.
Clemmesen J (1983)   The alleged association between artificial fluoridation of water supplies and
                    cancer: A review. Bull. WHO 61(5) pp 871-883.

GLOSSARY

NB. Terms are defined here within the context of this report only.

AGE DISTRIBUTION
The proportion of a population in different age-groups.

ASSOCIATION
A relationship between two events or characteristics. The relationship is not necessarily one of cause and effect.

CANCER
A group of diseases in which abnormal cells develop in a tissue or organ and grow in an excessive, uncontrolled and usually progressive fashion, characteristically forming an expanding mass of tumour at the site of origin. The mass invades locally and, at the same time, tumour cells are shed and disseminated to distant parts of the body to form separate secondary tumours.

CARCINOGEN
A general term for agents which cause cancer in man or animals. They comprise various extrinsic chemicals, physical agents such as ionising radiation and ultra-violet light, and certain viruses. Their causal role is complex and often involves interaction with other factors such as hormones.

CENTRAL CITY
A term used in United States censuses, and referring to an urbanised area with a population of 50,000 or more (in the 1960 Census) within a Standard Metropolitan Statistical Area (SMSA); each SMSA contains one or more central cities.

CORRELATION
Interdependence of events or characteristics. The *correlation coefficient* is a measure of the interdependence; that is, of the precision with which the value of one characteristic (e.g. fluoride level) can predict the value of the other (e.g. cancer rate).

CRUDE MORTALITY RATE
The total number of deaths in a given time interval, from all causes or from certain causes, divided by the total population at risk.

DEMOGRAPHIC FACTORS
The characteristics of a given population; in the restricted sense used in this report, it indicates the age, sex and racial distributions.

DIRECT STANDARDISATION
see Appendix 1.

EXTRAPOLATION
The estimation from an observed trend (q.v.), of the value of a variable (q.v.) outside the limits between which values are known. If the trend is represented graphically as a straight line, the extension of this line (from which values are then read) is called linear extrapolation.

FLUORIDATION
The addition of certain compounds of fluorine to water to produce a concentration close to 1 ppm of fluoride. Originally, sodium fluoride was used. This has now been replaced in most areas by hexafluorosilicic acid or sodium hexafluorisilicate.

FLUORIDE
A salt of hydrofluoric acid; the term is also often loosely applied to other compounds of fluorine. In this report, as in common usage, levels or concentrations of "fluoride" are quoted in terms of the fluoride ion $(F-)$ as measured by conventional techniques.

FLUORINE
A chemical element; normally present as a gas, or as part of a compound. The term is sometimes incorrectly used as a synonym for "fluoride".

HYPOTHESIS
A tentative theory to be tested.

INCIDENCE
The number of instances of illness commencing, or of persons falling ill, during a given period in a specified population. It is often used to denote the *incidence rate*, which is the number of instances per unit time divided by the number of persons in the specified population.

INDIRECT STANDARDISATION
see Appendix 1.

INTERCENSAL
Between census years.

INTERPOLATION
The estimation, from an observed trend (q.v.), of the value of a variable (q.v.) inside the limits between which values are known. The graphical representation of the trend as a straight line (from which the intermediate values are read) is called *linear interpolation*.

LATENT PERIOD
The time from the initiation of the biological process of cancer to its appearance clinically.

LINEAR
Represented graphically as a straight line (or capable of being so represented). See also Regression analysis.

MEDIAN
The middle value of a set of observations. Thus, of the other observations in the set, half are less than the median value, and half are greater.

MORTALITY
The number of deaths from a given cause in a given period in a specified population. It is often used to mean the *mortality rate*, which is the number of deaths per unit time divided by the number of persons in the specified population.

MULTIPLE REGRESSION ANALYSIS
Statistical technique for assessing the combined influence of a number of factors upon a particular outcome. (See also 'regression analysis').

NEGATIVE ASSOCIATION
A relationship between two events or characteristics, such that one decreases in magnitude as the other increases, and vice versa.

NON-FLUORIDATED
Not containing artificially added compounds of fluorine (q.v.). It is sometimes loosely used to distinguish water containing low natural levels of fluoride ion from water containing high natural levels.

PERICENSAL
Pertaining to a span of several years which includes a census year, and which is often centred on the census year.

POSITIVE ASSOCIATION
A relationship between two events or characteristics, such that one increases in magnitude as the other increases, and vice versa.

ppm
Parts per million; strictly milligrams (e.g. of fluoride) per kilogram (e.g. of water). As one litre of water has a mass of approximately one kilogram, it is essentially identical here to milligrams per litre.

PREVALENCE
The number of cases of a given disease in a given population at a designated time. The *prevalence rate* is this number divided by the number at risk.

REGRESSION ANALYSIS
A process for finding the mathematical description (within some restricted form, most commonly linear (q.v.)) which most accurately matches the relationship between a factor or factors and a particular outcome (that is, between two or more variables).

SMR
Standardised Mortality Ratio (see Appendix 1).

SRR
Standardised Registration Ratio. An index based on incidence rates (q.v.) and analogous to the SMR.

STANDARDISATION
See Appendix 1.

STATISTICAL SIGNIFICANCE
See Appendix 2.

SUB-GROUP
Part of a group, consisting of those members of the group with some factor(s) in common (e.g. age, sex, race).

TIME-TREND STUDY
A study which examines the trend (q.v.) in events (e.g. disease rates) occurring in a population over a number of years.

TREND

A movement (especially a long-term movement) in an ordered series of observations.

TREND-LINE

The graphical representation of a trend (q.v.) as a line drawn through a series of observations.

TUMOUR

A mass of abnormal cells which grow in an excessive and uncontrolled fashion. *Benign* tumours remain localised to the site of origin. *Malignant* tumours grow progressively, invade adjacent tissues and often spread to distant sites (see also 'cancer').

VARIABLE

Any quantity that varies (or may vary) in magnitude. Variables may be *dependent* on each other (that is, the value of one gives some information about the value of another), or *independent*.

WEIGHTING

A mathematical method of altering the relative influence of results from different sets of data, when these are pooled. When no such method is applied, the summary figure (e.g. the average) is said to be "unweighted" or "equally weighted".

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110

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REFERENCES

(The chapters of the report which cite each paper are indicated after the reference).

Austin D F (1975)   Memorandum dated October 21, 1975 to Chief, Family Health Services Section, State of California. *In* Hearings before a Sub-Committee of the Committee on Government Operations: The National Cancer Program: Part 2 — Fluoridation of Public Drinking Water. pp 394-399. Washington, 1977. (Chapters 6, 9).

Binder K (1977)   Untersuchungen über die Krebssterblichkeit in österreichischen Orten mit hohem und niederem natürlichen Fluoridgehalt im Trinkwasser. Öster Z Stomatol, 74(10), pp 355-360. (Chapters 2, 8, 9).

Biörck G, Boström H and Widström A (1965)   On the Relationship between Water Hardness and Death Rate in Cardiovascular Diseases. Acta Medica Scand 178(2) pp 239-252. Chapters 2, 8, 9).

Black G V and McKay F S (1916)   Mottled Teeth. Dental Cosmos 58 p 129. (Chapter 2).

Bradford Hill A (1977)   A Short Textbook of Medical Statistics. Hodder and Stoughton, London. (Chapters 1, 9).

Brady M (1977)   Is Fluoridation worth the risk? Cancer Control Journal 5 pp 157-158. (Chapters 2, 7, 9).

Buck C and Sellers A H (1960)   Mortality in Ontario municipalities in relation to the fluoride content of the water supply. Reported *in* Morden K G, Hall G E and Frankel E L (1961) Report of the Committee appointed to Inquire into and Report upon the Fluoridation of Municipal Water Supplies. Ontario. pp 89-90. (Chapters 8, 9).

Bunting R W, Crowley M, Hard D G and Keller M (1928)   Further studies of the relation of Lactobacillus acidophilus to detail carries III. Dental Cosmos 70 p 1002. (Chapter 2).

Burk D (1976)   Testimony and submissions to Hearings before a Sub-Committee of the Committee on Appropriations: Departments of Labour and Health, Education and Welfare Appropriations for 1977: Public Water Fluoridation. Washington 1976. (Chapter 4).

Burk D (1979a)   Fluoridation — cancer incidence linkage in England. Page proofs for Cancer Control Journal, submitted to meeting of the International Society for Fluoride Research, Oxford, September 1979. (Chapters 2, 7).

Burk D (1979b)   Cancer incidence and mortality linked to artificial water fluoridation. Article submitted to National Symposium on Water Fluoridation, Pretoria, October 1979. (Chapters 4, 7).

Burk D (1980)   Cancer mortality linked with artificial fluoridation in Birmingham, England. Paper submitted to 4th International Symposium on the Prevention and Detection of Cancer, London, July 1980. (Chapters 2, 4, 7, 9).

Burk D (1981)   Increased cancer mortality linked with artificial fluoridation of drinking water in large American and British Cities. Dean Burk Foundation, Washington. (Chapters 4, 7, 9).

Burk D and Graham J R (1984)   Summary Statement of Fact *re* The Fluoridation Cancer Link, February 1984. National Fluoridation News 29 *(4)* p4. *(Chapter 4).*

Burk D and Yiamouyiannis J (1975)   Letter dated July 8, 1975, to Hon. James J Delaney. *In Congressional Record, Proceedings and Debates of the 94th Congress. First Session. House of Representatives, July 21 1975. pp 23729-23732. (Chapters 2, 3, 6, 9).*

Burk D and Yiamouyiannis J (1976)   Fluoridation — linked Human Cancer based on time-trend mortality data. Abstract of paper presented at meeting of the International Society for Fluoride Research, Holland, February 1976. (Chapter 4).

Cecilioni VA (1977)   Letter dated August 27, 1977 to G Goldhammer. *In* Hearings before a Sub-Committee of the Committee on Government Operations: The National Cancer Program: Part 2 — Fluoridation of public drinking water. pp 258-261. Washington, 1977. (Chapters 8, 9).

Chilvers C (1982)   Cancer mortality by site and fluoridation of water supplies. J Epid and Comm Health 36(4) pp 237-242. (Chapters 2, 5, 9).

Chilvers C (1983)   Cancer mortality and fluoridation of water supplies in 35 US cities. Int J Epidemiol 12(4) pp 397-404. (Chapters 2, 4, 5, 9).

Chilvers C and Conway D (1985)   Cancer Mortality in England in relation to levels of naturally occurring fluoride in water supplies. J. Epid. Comm Health (in press) (Chapters 7, 9).

Cook-Mozaffari P, Bulusu L and Doll R (1981)   Fluoridation of water supplies and cancer mortality I: a search for an effect in the UK on risk of death from cancer. J Epid and Comm Health 35 pp 227-232. (Chapters 2, 7, 9).

Cook-Mozaffari P and Doll R (1981)   Fluoridation of water supplies and cancer mortality II: mortality trends after fluoridation. J Epid and Comm Health 35 pp 233-238. (Chapters 2, 7, 9).

Croce B (ed) (1892)   Napoli Nobilissima — a review of the Neopolitan Topography and Arts, Vol. I. (Chapter 2).

Dean H T (1938)   Endemic fluorosis and its relation to dental caries. Public Health Reports (US) 53 p 1443. (Chapter 2).

Dean H T, Arnold F A Jr, and Elvove E (1942)   Domestic water and dental caries V. Public Health Reports (US) 57 p 1155. (Chapter 2).

Department of Health, Education and Welfare (U.S.) (1970)	Fluoridation Census, 1969, Division of Dental Health, National Institutes of Health. (Chapter 3).
Department of Health, Education and Welfare (U.S.) (1975)	Statement dated April 25, 1975 by the National Cancer Institute on fluoridation studies by the National Health Federation. Bethesda. (Chapter 2).
Department of Health and Human Services (U.S.) (1984)	Fluoridation Census, 1980. Dental Disease Prevention Activity, Centres for Disease Control (Chapter 2).
Department of Health and Social Security, Scottish Office, Welsh Office, Ministry of Housing and Local Government (1969)	The fluoridation studies in the United Kingdom and the results achieved after eleven years. Reports on Public Health and Medical Subjects No. 122. HMSO London (Chapter 2).
Doll R and Kinlen L (1977)	Fluoridation of water and cancer: mortality in the USA. Lancet, June 18, 1977. pp 1300-1302. (Chapters 2, 4, 5)
Erhardt (1874)	Kali Fluoridatum zur Erhaltung der Zähne. Memorabil Mschr ration Aerzte Heilbronn 19 p 359. (Chapter 2).
Erickson J D (1978)	Mortality in selected cities with fluoridated and non-fluoridated water supplies. New Engl J Med 298 pp 1112-1116. (Chapters 2, 6, 9).
Fletcher J (1962)	Br Dent J 113 p 3-4. (Chapter 2).
Forrest J R, Longwell J, Stones H H and Thomson A M (1953)	The fluoridation of domestic water supplies in North America as a means of controlling dental caries. HMSO London. (Chapter 2).
Frederickson D S (1976)	Letter dated February 6, 1976 to Hon James J Delaney. *In* Hearings before a Sub-Committee of the Committee on Appropriations: Departments of Labour and Health, Education and Welfare Appropriations for 1977: Public Water Fluoridation. Washington, 1976. (Chapters 2, 4, 5).
Geever E F, Leone N C, Geiser P and Lieberman J (1958)	Pathologic studies in man after prolonged ingestion of fluorine in drinking water I. Necropsy findings in a community with a water level of 2.5 ppm. J Am Dent Assoc 56 pp 499-507. (Chapters 2, 6).
Glattre E and Wiese H (1979)	Inverse relationship between fluoride and cancer in mouth and throat? Acta Odontol Scand 37 pp 9-14. (Chapters 2, 8, 9).
Goodall C M, Foster F H and Fraser J (1980)	Fluoridation and cancer mortality in New Zealand, N Z Med J 92 pp 164-166. (Chapters 2, 8).
Graham J R and Burk D (1984)	Editorial Essay. Lord Jauncey and Justice Flaherty: Opposing views on the Fluoridation — Cancer Link. (Fluoride 17(2) pp 63-71. (Chapter 4).
Hagan T L, Pasternack M and Scholz G C (1954)	Waterborne fluorides and mortality. Public Health Reports 69 pp 450-454. (Chapters 2, 6, 7, 9).
Heasman M A and Martin A E (1962)	Mortality in areas containing natural fluoride in their water supplies. Mon Bull Minist Health 21 pp 150-160. (Chapters 2, 5, 7, 9).
Hoover R N (1977)	Statement in Hearings before a Sub-Committee of the Committee on Government Operations: The National Cancer Program: Part 2 — Fluoridation of Public Drinking Water pp 80-82. Washington, 1977. (Chapters 2, 5).
Hoover R N, Mason T J, McKay F W and Fraumeni J F (1975)	Cancer by county: new resource for etiologic clues. Science 189 pp 1005-1007. (Chapter 2).
Hoover R N and Mason T J (1975)	Memorandum dated March 5, 1975, to Director, Division of Dentistry, Bureau of Health Resources Development. *In* Hearings before a Sub-Committee of the Committee on Government Operations: The National Cancer Program: Part 2 — Fluoridation of Public Drinking Water pp 161-162. Washington, 1977. (Chapter 2).
Hoover R N, McKay F W and Fraumeni J F (1976)	Fluoridated drinking water and the occurrence of cancer. J Natl Cancer Inst 57 pp 757-768. (Chapters 2, 5, 6, 9).
IARC (1982)	International Agency for Research on Cancer, Monograph Volume 27 pp 279-303. Lyon. (Chapter 2).
Illinois, Department of Health, Bureau of Statistics (1952)	Mortality in fluoride and non-fluoride areas. Health Statistics Bulletin, Special Release No. 20. (Chapters 2, 6).
Jauncey, Lord (1983)	Opinion *in causa* Mrs Catherine McColl against Strathclyde Regional Council. The Court of Session. Edinburgh. (Chapters 2, 4, 7).
Kinlen L (1974)	Cancer incidence in relation to fluoride level in water supplies. Comm Health 6 pp 69-74. (Chapters 2, 6, 7, 8, 9).
Kinlen L (1975)	Cancer incidence in relation to fluoride level in water supplies. B Dental J 138 pp 221-224. (Chapters 2, 6, 7, 8, 9).
Kinlen L J, Clarke C A and Doll R (1980)	Fluoridation and cancer. Lancet, July 26, 1980. p 119. (Chapters 7, 9).
Kinlen L and Doll R (1977)	Cancer and Fluoride. Lancet, November 12, 1977. p1039. (Chapters 2, 5).
Kinlen L and Doll R (1981)	Fluoridation of water supplies and cancer mortality III: a re-examination of mortality in cities in the USA. J Epid and Comm Health 35 pp 239-244. (Chapters 2, 4, 5, 9).

Knizhnikov V A (1959)	The effect of water with a high fluorine content on the health of the adult population. Gig i Sanit 23(8) pp 18-23. (Chapters 2, 8, 9).
Knutson J W (1954)	An evaluation of the Grand Rapids Water Fluoridation Project. J Mich Med Soc 53 pp 1001-1006. (Chapters 2, 6).
Leone N C, Arnold F A, Zimmerman E R, Geiser P B and Lieberman J E (1955)	Review of the Bartlett-Cameron survey: a ten year fluoride study. J Am Dent Assoc 50 pp 277-281. (Chapters 2, 6).
Maritz J S (1980)	Statistics in examinations of association between fluoride in drinking water and cancer death rates. 5th Australian Statistical Conference, Sydney, August 1980. Australian Statistical Publishing Association. (Chapter 6).
Maritz J S and Jarrett R G (1983)	The use of statistics to examine the association between fluoride in drinking water and cancer death rates. Applied Statistics 32(2) pp 97-101. (Chapters 2, 4, 6).
Mason T J and McKay F W (1974)	US cancer mortality by county: 1950-1969. US Department of Health, Education and Welfare Publication No (NIH) 74-615. (Chapters 2, 3, 6).
McClure F J (1970)	Water fluoridation: the search and the victory. US Department of Health, Education and Welfare. (Chapter 2).
McCullough R S (1977)	Letter dated June 30, 1977 to Dr A I Cunningham. In Hearings before a Sub-Committee of the Committee on Government Operations: The National Cancer Program: Part 2 — Fluoridation of Public Drinking Water. pp 261-262. Washington, 1977. (Chapter 8).
McKenzie W J, Becker B J P, Dreyer C J, du Toit J, Dowdle E B D and de Graad J W (1966)	Report of the Commission of Inquiry into Fluoridation. The Government Printer, Pretoria. (Chapters 8, 9).
Ministry of Health, Scottish Office, Ministry of Housing and Local Government (1962)	The conduct of the fluoridation studies in the United Kingdom and the results achieved after five years. Reports on Public Health and Medical Subjects No. 105. HMSO London. (Chapter 2).
Mirisola F and Cruciani A (1964)	'Indagine Statistica sulla mortalita' in alcuni paesi del Lazio con acque naturalmente fluorate. Ann Stomat 13 pp 559-569. (Chapters 2, 8, 9).
Mohamed A H, Smith J D and Applegate H C (1966)	Cytological effects of hydrogen fluoride on tomato chromosomes. Can J Gen and Cytol 8 pp 575-583. (Chapter 2).
Morden K G, Hall G E and Frankel E L (1961)	Report of the Committee appointed to Inquire into and Report upon the Fluoridation of Municipal Water Supplies. Ontario. (Chapter 8).
National Academcy of Sciences (1977)	Drinking Water and Health. Washington (Chapter 2).
National Health and Medical Research Council, Australia (1979)	Submission to Committee of Inquiry into the Fluoridation of Victorian Water Supplies. (Chapters 2, 8).
Neuberger J S (1982)	Fluoridation and cancer: an epidemiologic appraisal. J Kansas Med Soc March 1982 pp 134-139. (Chapters 6, 9).
Newbrun E (1977)	The safety of water fluoridation. J Am Dental Assoc 94 (2) pp 301-304. (Chapter 6).
Nixon J M and Carpenter R G (1974)	Mortality in areas containing natural fluoride in their water supplies, taking account of socio-environmental factors and water hardness. Lancet, November 2, 1974 pp 1068-1071. (Chapters 2, 7, 9).
Okamura T and Matsuhisa T (1967)	The fluorine content in favourite foods of Japanese. Japan J Publ Health 14 pp 41-47. (Chapter 5).
Oldham P D and Newell D J (1977)	Fluoridation of water supplies and cancer: a possible association? Appl Stat 26 pp 125-135. (Chapters 2, 4, 5).
Oldham P D and Newell D J (1979)	Letter to the Editors. Appl Stat 28(2) P 184. (Chapters 2, 5).
Perkins C E (1952)	The truth about water fluoridation. 2nd edition. (Chapter 2).
Raman S, Becking G, Grimard M, Hickman J R, McCullough R S and Tate R A (1977)	Fluoridation and Cancer: an analysis of Canadian drinking water fluoridation and cancer mortality data. Department of National Health and Welfare. Ottawa. (Chapters 2, 8).
Richards G A and Ford J M (1979)	Cancer mortality in selected New South Wales localities with fluoridated and non-fluoridated water supplies. Med J Austral 2 pp 521-523. (Chapters 2, 8, 9).
Rogot E, Sharrett A R, Feinleib M and Fahsitz R R (1978)	Trends in urban mortality in relation to fluoridation status Am J Epid 107 pp 104-112. (Chapters 2, 6, 9).
Roholm K (1937)	Fluorine intoxication. H K Lewis, London (Chapter 2).
Royal College of Physicians (1976)	Fluoride, teeth and health. Pitmans, London. (Chapters 1, 2).
Schatz A and Schatz V (1972)	Use of compost instead of chemical fertiliser to avoid fluorine contamination of soil, water and food. Compost Science 13(2). (Chapters 2, 7, 9).
Schlesinger L R, Overton D E, Chase H C and Cantwell K T (1956)	Newburgh-Kingston caries fluorine study XIII: Pediatric findings after 10 years. J Am Dental Assoc 52 pp 296-306. (Chapters 2, 6).

114

Sheppard P M, Doll R and Kinlen L J (1976) — Fluoridation. Letter. New Scientist 69 p 304. (Chapter 7).

Shortt H E, McRobert G R, Barnard T W and Nayar A S M (1937) — Endemic fluorosis in the Madras Presidency. Indian J Med Res 25 p553. (Chapter 2).

Smith A H (1980) — An examination of the relationship between fluoridation of water and cancer mortality in 20 large US cities. N Z Med J 91 (661) pp 413-416. (Chapter 5).

Smith M C, Lantz E M and Smith H V (1931) — The cause of mottled enamel, a defect of human teeth. Univ Ariz Agr Expt Sta Bull 32. (Chapter 2).

Sognnaes R F (1979) — Historical Persepectives. In Johansen E, Taves D R and Olsen T O (eds): Continuing evaluation of the use of fluorides. AAAS Selected Symposium, Series II. (Chapter 2).

Stocks P (1958) — Cancer incidence in North Wales and Liverpool region in relation to habits and environment. Supplement to Part II of British Empire Cancer Campaign 35th Annual Report. pp 51-62. (Chapters 1, 9).

Strassburg M A and Greenland S (1979) — Health data on fluoride gets in depth probing. Water and Sewage Works, July 1979. pp 60-62. (Chapter 5).

Swanberg H (1953) — Fluoridation of water and its relation to cancer. Mississippi Valley Med J 75 pp 125-128 and 157. (Chapters 2, 6).

Taves D R (1977) — Fluoridation and cancer mortality. In Origins of Human Cancer, Book A: Incidence of cancer in humans. Cold Spring Harbour Conferences on Cell Proliferation, Vol 4. pp 357-366. (Chapter 2).

Taves D R (1979) — Claims of harm from fluoridation. In Johansen E, Taves D R and Olsen T O (eds): Continuing Evaluation of the Use of Fluorides. AAAS Selected Symposium, Series II. (Chapters 4, 5, 9).

Taylor A (1954) — Sodium fluoride in the drinking water of mice. Dental Digest 60 pp 170-172. (Chapters 2, 6).

Taylor A and Taylor N C (1965) — Effect of sodium fluoride on tumour growth. Proc Soc Exp Biol Med 119 pp 252-255. (Chapter 2).

Taylor E (1951) — Facts relative to rumours that fluoridation is harmful. Texas Dent J September 1951, pp 381-383. (Chapters 2, 6).

Walters C B, Sherlock J C, Evans W H and Read J I (1983) — Dietary intake of fluoride in the United Kingdom and fluoride content of some foodstuffs. J Sci Food Agric 34 pp 523-528. (Chapter 1).

Weaver R (1944) — Fluorine and dental caries: further investigations on Tyneside and in Sunderland. B Dental J 77(7) pp 185-193. (Chapters 2, 7, 9).

WHO (1958) — World Health Organisation Expert Committee on Water Fluoridation. First Report. WHO Technical Report Series No. 146. Geneva. (Chapter 2).

Wigle D T, Mao Y, Toft P and Meranger J C (1981) — Cancer mortality and drinking water quality in selected Canadian municipalities; preliminary results. In Proceedings of the Workshop on Compatability of Great Lakes Basin Cancer Registries, March 1981, Ontario. (Chapters 2, 8, 9).

Winner F V, Walther F O and Graham J R (1978) — Plaintiff's memorandum of law and summation of evidence in favour of a preliminary injunction. Court of Common Pleas of Allegheny County, Pennsylvania: Civil Division. No D G 4585-78. (Chapters 2, 4, 5).

Yiamouyiannis J (1975a) — Cancer death rate highest in fluoridated cities. Reprint 3H/7L National Health Federation, Monrovia, California. (Chapters 2, 3, 6, 9)

Yiamouyiannis J (1975b) — Cancer death rate in fluoridated cities. Reprint 3H/7L (revised). National Health Federation, Monrovia, California. (Chapters 2, 3, 6, 9).

Yiamouyiannis J (1975c) — Fluoride and cancer. National Health Federation Bulletin, April 1975 pp 9-11. (Chapters 2, 6).

Yiamouyiannis J (1975d) — A definite link between fluoridation and cancer death rate. National Health Federation. March 25, 1975. (Chapters 3, 6, 9).

Yiamouyiannis J (1977) — Prepared Statement to Sub-Committee of the Committee on Government Operations: The National Cancer Program: Part 2 — Fluoridation of Public Drinking Water pp 61-72. Washington, 1977. (Chapters 2, 4).

Yiamouyiannis J (1978) — Cancer mortality and fluoridation. Lancet, January 21, 1978, p 150. (Chapters 2, 4).

Yiamouyiannis J (1979) — Fluoridation and cancer: a review of human epidemiological studies. National Health Federation, Monrovia, California. (Chapters 4, 5, 6).

Yiamouyiannis J (1980) — Letter dated 6 February 1980, with attached tables, to official at DHSS. (Chapters 2, 4).

Yiamouyiannis J and Burk D (1975) — Letter dated December 11, 1975, to Hon. James J Delaney. In Congressional Record, Proceedings and Debates of the 94th Congress, First Session. House of Representatives. December 15, 1975 pp 40773-40775. (Chapters 2, 3, 4).

Yiamouyiannis J and Burk D (1977) — Fluoridation and cancer: age-dependence of cancer mortality related to artificial fluoridation. Fluoride 10(3) pp 102-123. (Chapters 2, 3, 4, 5, 9).