Critical appraisal of “Fluoride in Drinking Water: A Scientific Review of EPA’s standards”

A report for South Central Strategic Health Authority
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Contents

1. Executive Summary ................................................................. 2
2. Scope and methods of the critical appraisal........................................ 2
3. Overview.................................................................................. 3
    Chapter 1: Introduction ................................................................ 5
    Chapter 2: Measures of Exposure to Fluoride in the United States ......... 11
    Chapter 3: Pharmacokinetics of fluoride .......................................... 15
    Chapter 4: Effects of fluoride on teeth ............................................. 18
    Chapter 5: Musculoskeletal effects .................................................. 22
    Chapter 6: Reproductive and developmental biology........................... 27
    Chapter 7: Neurotoxicity and neurobehavioural effects ....................... 30
    Chapter 8: Effects on the endocrine system ..................................... 34
    Chapter 9: Effects on the gastrointestinal, renal, hepatic, and immune systems .... 37
    Chapter 10: Genotoxicity and Carcinogenicity.................................... 41
    Chapter 11: Drinking water standards for Fluoride .............................. 45
4. References................................................................................ 48
5. Abbreviations and Acronyms ...................................................... 49

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Bazian Ltd
10 Fitzroy Square
London W1T 5HP
Phone: +44 (0) 20 7874 1594
Contact email: info@bazian.com
1. Executive Summary

This book was published by the National Academies Press in 2006. Its purpose was to review the Environmental Protection Agency’s (EPA) drinking water standards for fluoride in drinking water, including the maximum permissible level of 4mg/L (equivalent to 4ppm), to determine whether they were likely to prevent adverse health and cosmetic effects. In order to do this the book reviewed research on the health effects from exposure to fluoride published since their last review of these standards in 1993, in the context of the existing evidence.

The book concludes that setting the Environmental Protection Agency’s (EPA) drinking water standard for fluoride at a maximum of 4mg/L (equivalent to 4ppm) does not adequately protect against adverse health effects, and the authors recommend that this maximum permissible level should be lowered.

In our assessment we found that the methods used by the book’s authors had some important limitations and that the question it examines does not have direct relevance to the issue of fluoridation in Southampton.

Specifically:
- The book was not a systematic review. The gold standard way of addressing questions about the effects of exposure is by using a systematic review, as this ensures that all evidence is identified and assessed in a transparent way using replicable methods.
- The maximum levels of water-borne fluoride for cosmetic or health safety recommended by the EPA, and examined in the book, are two to four times higher than the level of water fluoridation proposed for Southampton and higher than the 1.5ppm maximum level laid down by the European Union.
- The purpose of this book was to assess the risks of environmental contamination with fluoride at the maximum levels recommended by the EPA, and not to assess the health effects of water fluoridation schemes.

2. Scope and methods of the critical appraisal

Bazian have critiqued the National Research Council of the National Academies (NRC) book “Fluoride in Drinking water: A Scientific Review of EPA’s Standards”. This appraisal specifically aimed to determine the relevance of this book to Southampton, where artificial fluoridation of the public water to a target level of 1ppm (1mg/L) of fluoride is proposed using hexafluorosilicic acid.

We have summarised and critiqued the overall purpose and methods used in preparing the NRC’s review with reference to the validity of their methods, and applicability to Southampton.

We have also critiqued the findings from each chapter, concentrating on chapters 4-10 (which examine specific risks). Where possible we have identified the study types, and discussed the validity and applicability of these types of evidence to the South Central SHA’s policy decision.

Note that within the available timeframe, individual critical appraisal of each study identified within the book was not possible. Critiques of key individual studies based on the information provided in the review have been used to illustrate key limitations or strengths of the evidence.
It is beyond the scope of this report to assess the evidence behind the EPA’s original recommendations or the NRC’s 1993 review, except for the research that is discussed again in this book.

In the preparation of this report, Bazian expresses its own independent assessments and judgements, based on its evidence-based critique of the documents. No other parties have been permitted editorial or consultative input into Bazian’s assessment.

3. Overview

Summary of book’s conclusions

Based on the information identified in their review, the committee unanimously decided to recommend that the MCLG be lowered from 4mg/L. The basis for this was that:

- children exposed to 4mg/L drinking water fluoride (the MCLG) are at risk of severe enamel fluorosis, which involves enamel loss and pitting
- it would reduce lifetime accumulation of fluoride in the bone which the majority of the committee (nine out of twelve) thought likely to increase and individual’s risk of fracture and possibly skeletal fluorosis. Three members of the committee felt that more evidence was needed to determine whether fractures occur at an appreciable rate at 4mg/L.

Summary of Bazian’s critique of the book (validity and applicability)

There are a number of limitations to the applicability of the findings in this book to the South Central SHA’s decision:

- The book did not aim to determine the risks or benefits of artificial water fluoridation, or to recommend appropriate levels for artificial fluoridation.
- The book specifically focussed on assessing whether the current maximum guideline levels for naturally occurring fluoride in drinking water as set by the EPA were sufficient to avoid public health risks, based on evidence published since the last NRC review of these levels in 1993. Only the health risks of fluoride were assessed in this review, any health benefits were not considered.
- The levels of fluoride exposure assessed by the book (4mg/L and 2mg/L, the EPA’s maximum contaminant level and secondary maximum contaminant level respectively) are two to four times higher than the target level of fluoridation proposed by the South Central SHA (1mg/L). Harms judged to be attributable to these higher levels of exposure are not directly applicable to the proposed levels of fluoridation in Southampton (1mg/L).
- Although individual studies which were conducted in areas with fluoride at or near 1mg/L in drinking water were cited in the book, these were a by-product of looking for studies relevant to the higher concentrations assessed, and may not represent the full body of evidence relevant to the SHA’s policy decision. These studies did not convincingly indicate harm at 1mg/L fluoride in drinking water.
- Based on the evidence provided the book, the harms on which the committee based its decision to suggest lowering the MCLG (severe enamel fluorosis, bone fractures, or stage II or III skeletal fluorosis) are not likely to apply at the lower concentration of 1mg/L.

In terms of the general validity of the book’s findings the following points are important to note:

- The book was not a systematic review, as it did not use systematic review methods to identify and assess the evidence about potential harms of fluoride in drinking water, nor did
it provide an audit trail of studies identified or those included and excluded, with the reasons.

- The book represented a narrative discussion of studies identified by the committee that were published since the 1993 review, plus key studies published previously.
- The method used by the committee in identifying information was democratic, in that they allowed submission of evidence from any party and it was all given consideration, but this approach is not systematic.
- Use of systematic review methods ensures that all applicable evidence is identified through systematic searching of literature databases, and that all research is assessed against pre-determined inclusion and exclusion criteria designed to ensure that all studies are assessed in an unbiased way, and that included studies are of sufficient quality and sufficiently relevant to the question addressed. A systematic approach allows a clear audit trail of studies identified, included and excluded.

- The book did not report how many studies were identified, how many included and excluded by the committee, and on what basis. It was not stated if the literature presented in the book represented all of the information considered in making their decision, or just key studies that illustrated what points were considered.

- The committee used a “weight-of-evidence” approach to help them come to a consensus decision about whether the evidence supported the existence of key harms, and their recommendations with regard to the EPA’s guideline levels. However, no transparent methods for weighing up evidence from different sources included (mechanistic information, in vitro studies, animal studies, and human studies) was provided.

- The book did not describe use of standard criteria to decide whether the research studies it identified were reliable and relevant. Consequently, the underlying studies included were of variable reliability for answering the questions asked.

- This review included mechanistic information, animal studies, and in vitro studies. Such information is useful in hypothesis generation about what effects might be seen in humans, explaining and investigating effects in humans, and ruling out extreme toxicity. However, evidence from non-human studies and mechanistic reasoning can be misleading when used as a rationale for predicting response in humans, and evidence from human studies should be given precedence over other kinds of evidence, where it exists.

- There was no discussion that directly linked the concluding statements to the underlying evidence. As the conclusions were based on studies of a variety of designs, varying reliability and applicability, the way in which these links are made is important. In this book it was not possible to tell how the authors had rated the quality and quantity of evidence and therefore to assess the ‘strength’ or level of confidence that the reader should have in their conclusions.
Chapter 1: Introduction

Key messages
This section reports on the background to the NRC’s book and also the methods they used in preparing their review. We summarise the background information, as it informs interpretation of the findings of the report; we did not specifically critique this background information. We also summarise and critique the methods of the review. In our discussion of Chapter 1, we have also included relevant information from the Preface, Summary, and Appendix A (Biographical Information on the Committee on Fluoride on Drinking Water).

The aim of this book was to review the US Environmental Protection Agency’s (EPA) guideline levels for naturally occurring fluoride in drinking water (maximum contaminant level goal [MCLG] of 4mg/L and secondary maximum contaminant level [SMCL] of 2mg/L). It did not aim to assess the safety or benefits of artificial fluoridation. As such, this book is not directly relevant to the South Central SHA’s policy decision about artificial fluoridation at a level of 1mg/L.

This book was not a systematic review, as it did not use systematic review methods to identify and assess the evidence about potential harms of fluoride in drinking water, nor did it provide an audit trail of studies identified or those included and excluded, with reasons. Systematic reviews are the gold standard level of evidence for answering questions about the effects of exposures, as they ensure that all evidence is identified and assessed in a transparent way using replicable methods.

The approach used in the book involved assessing multiple sources of information including mechanistic information, in vitro studies, animal studies, and human studies. The book reported using a “weight-of-evidence” approach to come to consensus decisions about the effects of fluoride, but no transparent methods for weighing up the evidence from the different categories was provided. It was not possible to identify the quality and quantity of evidence behind each of the conclusions, and therefore the ‘strength’ of these conclusions and the level of confidence that a reader should have in them.

Summary of ‘background’
The NRC’s review was supported by a contract between the National Academy of Sciences and the US Environmental Protection Agency (EPA). The National Academies (NA of Science, NA of Engineering, Institute of Medicine, and National Research Council) bring together committees of experts in all scientific and technical areas to provide advice to the government and the public about issues of national importance.

The EPA sets maximum permissible levels of contaminants that may cause human health risks in public drinking water systems in the US. For each contaminant it sets a maximum contaminant level goal (MCLG), which is the “concentration at which no known or expected adverse health effects occur and the margins of safety are adequate”. The MCLG is not enforceable, but it is used to set the maximum contaminant level (MCL), which is enforceable. The MCL is set as close to the MCLG as is technically feasible. The EPA may also set a secondary maximum contaminant level (SMCL) for a contaminant, which is a “non-enforceable guideline for managing drinking water for aesthetic or technical effects related to public acceptance of drinking water”.

The NRC was commissioned to review the EPA’s MCLG and SMCL for fluoride in drinking water, to determine if they were adequate to protect public health. The review was part of the regular review
of regulations regarding drinking water contaminants (a legal requirement of the US Safe Drinking Water Act), and as a result of new research having been carried out since the last review in 1993.

The MCLG of 4mg/L (or 4ppm) and SMCL of 2mg/L for fluoride were set by the EPA in 1985-1986. The MCLG aimed to prevent crippling skeletal fluorosis, and was based on an estimation of how much fluoride a person would need to ingest to develop crippling skeletal fluorosis (estimated at 20mg/day) with an extended period of exposure, how much water an adult drinks a day (estimated at 2L/day), and inclusion of a safety margin (a factor of 2.5) to reduce the likelihood of error (i.e. 20mg/day +2L/day=2.5=4mg/L). The MCLG and MCL for fluoride are the same (4 mg/L). The SMCL was set to avoid objectionable enamel fluorosis, and was based on a review of data that found that at exposures of 2mg/L, moderate fluorosis (visible brown staining) occurred in between 0 and 15% of those exposed, and severe cases (yellow to brown staining and pitting and cracking of the enamel) only occurred at 2.5mg/L or more. Drinking water providers whose drinking water exceeds the SMCL need to notify their customers of the risk of enamel fluorosis. The NRC reviewed the MCL in 1993 and concluded that this was an appropriate interim level, but that further research was needed.

The EPA’s MCLG, MCL, and SMCL are set to control the amount of naturally occurring fluoride in drinking water. They are not intended to be recommendations about artificially fluoridating drinking water to prevent dental caries. The NRC review does not address the benefits, safety, or efficacy of artificial fluoridation, but artificial fluoridation was assessed as a source of fluoride exposure.

Fluoride is drinking water comes from both natural and artificial sources. Natural sources include fluoride compounds naturally found in rocks and soil, as well as from industrial processes, such as coal burning. The level of naturally occurring fluoride varies from area to area in the US, with levels as high as 11 to 15.9mg/L in some areas.

Fluoride is also added to the water to prevent dental caries in some areas of the US, a process which has been carried out since 1945. Dental caries is caused by bacteria on the surface of the tooth which ferment carbohydrates and produce lactic acid and other acids that eat away at the enamel and make a cavity, which can then lead to toothache, abscess formation, damage to the bone underlying the tooth and systemic infection if left untreated.

Limits for safe water fluoridation in the US were set by the US Public Health Service at between 0.7 to 1.2 mg/L. The higher limit applies to cool areas, where people drink less water, and the lower limit applies to warm areas, where people drink more. State or local authorities decide whether or not to fluoride drinking water, and almost two thirds of the population were estimated by the US Centers for Disease Control and Prevention (CDC) to receive optimally fluoridated water in 2000.

Silicofluorides are reported to be the most common form of fluoride added to water for artificial fluoridation in the US. These chemicals have been assumed to dissociate in water and therefore have similar toxicity to fluoride salts (such as those used in dental products), and therefore there has been limited data on their effects. This assumption has been questioned.

The addition of fluoride to drinking water has always been controversial, with questions raised about:

- motivation for fluoridation
- safety of fluoride and silicofluorides
- infringement of personal choice
- whether dental benefits outweigh risks
- difficulty in ensuring appropriate individual doses
• whether the dental benefits are associated with topical rather than systemic use.

However, the book reports that public health bodies dispute these claims, and that several bodies have concluded that water fluoridation prevents dental caries. Water fluoridation is supported by the CDC, and has been endorsed by each US Surgeon General.

Summary of ‘Committee’s Approach’
The NRC assigned the task of reviewing the EPA’s MCLG and SMCL to the standing Committee on Toxicology, which assembled the expert committee (Committee on Fluoridation of Drinking Water) who prepared the report. This committee had 12 members; the chair was an emeritus professor in pharmacology and toxicology, and other committee members were experts in the areas of reproductive biology, toxicology, dentistry, preventive dentistry, behavioural neuroscience, cancer epidemiology, dental public health, epidemiology, orthopaedics, risk analysis, and environmental health.

The committee aimed to review:
• clinical, epidemiologic, and toxicologic data on fluoride with emphasis on data published since the previous review (1993)
• exposure data on the effects of fluoride consumption in drinking water and other sources
• the scientific basis for the EPA’s MCLG and SMCL
• the adequacy of these levels for protecting children and adults from adverse effects

They also aimed to:
• consider the contribution of different sources of fluoride (such as drinking water, food, and dental hygiene products)
• identify gaps in the data
• make recommendations about what research might be carried out in the future to support setting of the MCLG and SMCL

They did not consider questions about:
• possible health risks from lack of fluoride exposure
• the effects of fluoride on preventing dental caries
• economic evaluations
• risk-benefit analyses
• water treatment technology

The committee held six meetings. The first two meetings included data collection, and were open to the public. The EPA, Centres for Disease Control and Prevention (CDC), people involved in fluoride research, and fluoridation supporters and opponents all made presentations to the committee. The committee reviewed submissions from a variety of sources; these submissions included research articles, literature reviews, position statements, and unpublished data. The committee reported that they considered each piece of data “on its own merits” and “case by case”. They concentrated on research completed since their previous report (1993).

They looked at data relating to:
• pharmacokinetics (Chapter 3)
• dental effects (Chapter 4)
• skeletal effects (Chapter 5)
• reproductive and developmental effects (Chapter 6)
• neurological and behavioural effects (Chapter 7)
• endocrine effects (Chapter 8)
• gastrointestinal, renal, hepatic and immune effects (Chapter 9)
• genotoxicity (potential to damage genetic material) and carcinogenicity (Chapter 10)

They used a “weight-of-evidence” approach, in which they determined whether “multiple lines of evidence indicate a human health risk”. They assessed a wide range of evidence, including:
  • in vitro assays
  • animal studies
  • human studies
  • mechanistic information (the patho-physiological reasoning about how fluoride might have an effect)

They say that they included positive and negative results, and considered the data in light of the exposures that would occur with drinking water containing the MCLG or SMCL of fluoride. They also took into account the dose and time of exposure (both frequency and duration). They also attempted to identify subgroups of the population that might be at greatest risk.

Based on the data they analysed, they prepared a draft report, which was independently reviewed by selected experts from wide ranging fields. These experts included individuals from research institutes and universities, mainly from the US, and an international multinational scientific and regulatory consulting firm. A final draft was reviewed by a further two individuals from US universities who ensured compliance with the NRC’s independent review procedures.

Bazian’s critique of committee’s approach (validity and applicability)
The expert committee used democratic methods to collect information, allowing submissions from all sources, including supporters and opponents of fluoridation, and including positive and negative results. It formulated recommendations by consensus and the draft report was peer reviewed by experts. This does not qualify as a systematic review.

A systematic review clearly defines the question(s) to be addressed, and carries out systematic searching of literature databases to identify all relevant literature. All of the literature is then assessed against a set of pre-determined inclusion and exclusion criteria to identify and include only the most reliable and relevant research in an unbiased and reproducible way. All of the literature that meets inclusion criteria is then analysed to come to a conclusion about the question asked. This systematic approach avoids potential biases and allows a clear audit trail of studies identified, included and excluded. In addition, fully describing methods ensure that the results of a systematic review are replicable. As such, systematic reviews are considered the gold standard level of evidence for answering questions about the benefits and harms of exposures, such as medical treatments or environmental exposures such as fluoride.

Although the book represents the agreed consensus of the committee based on the evidence they received, the lack of a systematic approach means that relevant studies may have been missed and decisions about inclusion or exclusion of studies may not have been made in a standard way. In addition, because there was no standard way of dealing with studies, it was not possible to determine whether the literature presented in the book represented all of the information considered in making the committee’s decision, or just key studies that illustrated best the points that were considered. Some studies were used as references for statements in the text without full description of their methods, and it often was difficult to identify the study design of such studies.

Systematic reviews usually limit themselves to including only those studies whose designs are the most appropriate for answering the question posed. For example, systematic reviews looking at
treatments would usually aim to only include randomised controlled trials (RCTs) as this is the study design least susceptible to bias. Lower levels of evidence (such as observational evidence) might then be included if no RCTs were identified.

This review included a wide range of evidence, including mechanistic information, in vitro studies, studies in experimental animals, as well as studies in humans. There was no clearly defined hierarchy of evidence, which defined which types of evidence carried more weight than others.

In questions about human health, studies in humans are the most applicable and reliable. Although mechanistic information can identify potential effects of a chemical, mechanistic arguments passed on pathophysiological principles and reasoning do not always prove to be correct. Likewise, tests in vitro and in animals do play a role in identifying possible beneficial and adverse effects of chemicals. However, the differences between single cells or tissues grown in the laboratory and the human body as a whole, and inter-species differences between laboratory animals and humans, mean that these types of evidence may also inaccurately predict benefits and harms in humans. Therefore, in this review, where human studies are available, this should be given the greatest weight.

Studies in humans can also be further subdivided into different study types. The lack of set inclusion and exclusion criteria based on the reliability of studies mean that studies of varying designs and reliabilities were included. These different study types have different biases and limitations.

As mentioned above, the highest level of evidence about the effects of a treatment is obtained from RCTs, as random allocation of individuals into groups ensures balance between these groups, so that the only difference between the groups will be the treatment being tested. However, in some cases carrying out an RCT is impractical or unethical, and observational studies are then the best available evidence. In observational studies, researchers do not assign people to groups, instead people naturally fall into groups, and then information about their exposures and outcomes are examined by the researchers. There are a number of different types of observational studies, such as cohort studies, ecological studies, case-control studies, cross sectional studies, case series and case reports.

The main limitation of observational studies is that groups of exposed and unexposed individuals are likely to differ in factors other than exposure, and these differences can affect the outcomes seen, leading to the outcomes being incorrectly attributed to the exposure. This is called confounding. This problem can be limited by taking measures to ensure that the groups to be compared are as similar as possible or identifying differences between the groups in potential confounders and taking them into account when analysing the results. Studies that collect information about individuals’ exposures and potential confounders in a prospective way, before an outcome occurs, offer the best chance of avoiding confounding. Not all potential confounders may be known, and because making adjustments may not be enough to remove their effect, there may still be residual confounding. However, reliability of observational studies is increased by assessing and adjusting for potential confounders.

Most of the observational studies in this book had an ecological (or partially ecological) design. Ecological studies look at exposures and outcomes at the population level. For example, a study could look at communities with different fluoride levels and compare how often a certain outcome (e.g. kidney stones) occurred in the communities to assess whether fluoride is having an effect. However, people’s individual exposures and outcomes are not known, so it is not possible to confirm that all individuals in the high exposure group were exposed to the same levels of fluoride, and that these levels were higher than those people in the lower exposure group. Confounding is also a problem, as
although some adjustments for population level confounders can be made, such as average income, it
is not possible to adjust for individual level confounders, such as family history of a disease.

In partially ecological studies, exposures are assessed at the population level and outcomes are
assessed at the individual level. This design allows adjustment for some individual level confounders,
but again does not allow assessment of individual exposures. Ideally fully individual level studies such
as cohort studies would be used to support ecological data.

Other study designs are susceptible to different biases and have their own limitations. Prospective
cohort studies are considered to be the most reliable form of observational evidence when looking at
causation. This is because they set out to collect information on each individual’s exposures and
outcomes as they occur, rather than assessing events that have already happened. They ensure that
exposures precede outcomes, a temporal sequence that must exist in order for the link to be
considered causal. They also provide the opportunity of collecting data about potential confounding
factors for each individual, which allows adjustment for these factors in analysis of results. In
addition, collection of individual exposure data means that dose-response relationships can be
investigated. Few studies included in the book were prospective cohort studies.

Cross sectional studies collect information about exposures and outcomes at one time point. This
means that they do not provide any information about the temporal sequence of exposures and
outcomes, which limits their usefulness in reliably determining causation. An exposure has to precede
an outcome in order for it to be a plausible cause of the outcome.

Case-control studies compare exposures in people with and without a disease. As this design assesses
past exposures, there can be problems with the accuracy of recall. In addition, cases may have
systematic differences in how they remember their exposures, particularly if they think there may be
a link between the exposure and their disease. Case control studies may also suffer from selection
bias, where cases are not representative of all people with the disease, or controls are not similar
enough to the cases.

Case series are studies looking at a group of individuals which a particular characteristic (e.g. all with
a specific exposure, or disease) and case reports look at single individuals. The lack of a control group
in these studies means that a link between exposure and outcome cannot be proven, as there are not
comparator individuals who were not exposed or who do not have the disease of interest.

Within each study type there can also be variability in the reliability of individual studies, and this
should be taken into account in a systematic review.
Chapter 2: Measures of Exposure to Fluoride in the United States

Key message
This chapter discusses exposure to fluorides in people living in the US. It looks at data regarding exposure from various sources and their relative importance in different age groups. It also looks at what factors could affect an individual’s exposure and identifies subgroups who might experience greater exposure.

Most of the evidence in this chapter comes from human studies and surveys of fluoride content in foodstuffs or other products. The study designs of these studies or details of their methods were not always presented, making it difficult to judge the reliability of these studies.

The chapter provides estimates of total exposures to fluoride in the US population; these estimates come from a variety of sources and are based on various assumptions. The reliability of these estimates will rely on the accuracy of the underlying sources and on the assumptions made. Figures are presented for total exposures to fluoride if drinking water contains 1mg/L fluoride, which is the level proposed for use in the Southampton. Many of the figures underlying these estimates come from US specific sources; estimations of fluoride intake based on UK sources would be more relevant to the UK setting.

Summary of ‘Findings’
This chapter and the book’s summary conclusions regarding exposure, say that:

- The major sources of exposure in the US are drinking water, food, dental products, and pesticides, with drinking water being the largest contributor
- About 1.4 million people in the US had drinking water concentrations of natural fluoride of 2.0 to 3.9mg/L and just over 200,000 had levels ≥4mg/L according to 1992 estimates
- In 2000, about 162 million people in the US had artificially fluoridated water containing 0.7 to 1.2mg/L fluoride
- Food sources are the second largest contributors of fluoride exposure (mainly beverages), followed by dental products, mainly toothpastes
- Other sources include fluoride in the air, from pesticide residues, pharmaceuticals, and consumer products
- Highly exposed populations include those who:
  - have high fluoride levels in their drinking water
  - drink large volumes of water, such as athletes, people with certain medical conditions, and outdoor workers
  - have exposure to other sources of fluoride
- Children and infants are also reported to have about three to four times the fluoride exposure of adults per unit bodyweight. They may have more exposure to fluoride from dental products because they tend to use more toothpaste than recommended, may swallow more toothpaste than adults, and may receive fluoride treatments from their dentist
- The proportion of a person’s total fluoride consumption that comes from drinking water was estimated by the committee to range from 57% to 94% depending on age and level of drinking water fluoridation (2mg/L or 4mg/L), this increases to 86% to 98% among those who drink higher levels of water
- Infants and children have the greatest intake per kilogram of bodyweight (0.079 to 0.258mg/kg/day with 4mg/L fluoride in drinking water, and 0.046 to 0.144mg/kg/day with 2mg/kg/L)
• For those with high water intake drinking water with 4mg/L fluoride daily exposure ranges from 0.294mg/kg/day for adults to 0.634mg/kg/day for children, and with 2mg/L fluoride daily exposure ranges from 0.154mg/kg/day for adults to 0.334mg/kg/day for children

• Historically a daily intake of 4-5mg by an adult (about 0.06 to 0.07mg/kg/day in an average 70kg adult) was considered a “health hazard”, but more recent estimates from the US Institute of Medicine have suggested that 10mg/day (0.14mg/kg/day for the average adult of 70kg) is a tolerable upper limit for anyone aged over 8 years old, although this level has been associated with a possibility of mild skeletal fluorosis, or even crippling skeletal fluorosis in other reports

• The recommended optimum level of fluoride intake in children to get the maximal reduction in dental caries with minimum likelihood of enamel fluorosis is often reported to be 0.05 to 0.07mg/kg/day, but the initial origin of this figure is unclear

• The committee estimated average fluoride intake from all sources (including drinking water at 1mg/L) as:
  – 0.07mg/kg/day in all infants aged less than 1 year (about 0.03mg/kg/day in nursing infants and between 0.08 and 0.09mg/kg/day in non-nursing infants)
  – between about 0.06 and 0.07mg/kg/day in children aged 1 to 5 years
  – about 0.04mg/kg/day in people aged 6 to 12 years
  – about 0.03mg/kg/day in people aged 13 years and above

• The reported optimal levels (0.05 to 0.07mg/kg/day) are reached or exceeded if water contains 4mg/L fluoride, and also in certain high intake groups at lower water fluoride levels

• Although a number of researchers have pointed out the importance of individual measurement of fluoride intake from all sources, they have also noted the difficulties of this, including the variability in levels in various foods and drinks, and also the variability of people’s intakes of these items.

• They report that for the majority of people the most important part of their fluoride intake (about 50% or more) comes from fluoridated water and beverages and foodstuffs made with fluoridated water

Bazian’s critique of this chapter (validity and applicability)

Little information was provided about the studies from which figures were quoted; therefore it was difficult to assess their study designs and validity. Some exposures are reported from cross sectional studies and surveys measuring fluoride in different items such as foodstuffs. National figures about drinking water in the US (e.g. proportion of people receiving fluoridated water, levels of fluoride in water) came from the US Centers for Disease Control and Prevention (CDC), a reliable source.

Average per capita ingestion of community water in the US was based on EPA survey of 15,000 people, and was estimated at just less than 1L a day, with the 90th percentile being 2L. The review did not compare water consumption in other settings, so it is not clear to what extent these figures are representative of what happens in the UK.

Other differences between the US and UK settings relating to drinking water include:

• The maximum level of fluoride allowed in drinking water is the UK is 1.5mg/L, whereas the maximum level permissible in the US is 4mg/L (the MCL), with public notification required if levels exceed 2mg/L. Figures from the UK Department for Environment Food and Rural Affairs (DEFRA) suggest that in England and Wales in 2004-2007 levels of fluoride in public water ranged up to 1.5mg/L, with the majority of the country receiving water with levels between 0 and 0.49mg/L. Because permitted fluoride levels are lower in the UK, this may reduce the contribution of drinking water to overall fluoride intake
• Artificial fluoridation in the UK is required to be maintained at 1.0mg/L as far as is practicable, optimal levels for artificial fluoridation in the US are described as 0.7 to 1.2mg/L depending on the climate
• The proportion of people receiving artificially fluoridated water is much lower in the UK than in the US, with figures from DEFRA reporting that only 10% of the population in the UK are estimated to receive artificially fluoridated water, whereas it was about 58% in the US population in 2000 based on figures presented in the NRC review and US census figures
• Although the majority of US water fluoridation uses the fluorosilicates (75% of water systems), sodium fluoride is also used. In the UK, only fluorosilicates (hexafluorosilicic acid and disodium hexafluorosilicate) are permitted, and for Southampton hexafluorosilicic acid is proposed
• The proportion of people using water from non-public sources in the US and UK may differ, with about 12.5% of the US population estimated as having non-public sources of water

In general, the US would seem to be more representative of the UK setting in terms of lifestyle than countries with very different cultures and with very different socioeconomic status (such as China or India). Estimates of the relative proportions of fluoride consumed from different sources in the US would ideally need confirmation in the UK.

Regarding the conclusions drawn about meeting the reported “optimal” levels of fluoridation for maximising caries prevention and minimising fluorosis (0.05 to 0.07mg/kg/day), it is important to note that exceeding these does not necessarily imply a health risk. The review reports that the initial origin of these “optimal” figures is unclear; therefore their validity is also unclear.

The estimates of total fluoride exposures are based on pesticides (sulfuryl fluoride and cryolite), background food, toothpaste, fluoride supplements, air and water. The figures for sulfuryl fluoride, cryolite, background food, and air were based on an exposure assessment by the EPA in 2004. The figures for supplements were taken from the American Dental Association (ADA). Toothpaste ingestion was based on one study from 1995. Water consumption was based on a complex model called the DEEM-FCID model, which included data from surveys in 1994-1996 and 1998. This model takes into account direct exposure to drinking water, as well as indirect exposures to water via food and beverage products produced with water. As an alternative, water consumption was also estimated using the EPA’s default daily values of 1L for a 10kg child and 2L for a 70kg adult.

It is important to note that the data on population intakes are estimates. The accuracy of these estimates depends on the accuracy of the underlying data and the assumptions made. These data came from multiple sources and may not be applicable in the UK setting, as many were taken from US specific sources, such as the EPA and ADA.

Silicofluorides
This chapter reports that silicofluorides have been reported in some studies to be associated with elevated blood concentrations of lead, and says that this link is potentially related to incompletely dissociated silicofluorides remaining in the water or to the leaching of lead into drinking water in systems that use chloramines (a type of disinfectant). Another study is said to have looked at blood lead concentrations in children exposed to fluoridated water. This study’s authors said that their analysis did not support an association between silicofluorides and blood lead, but could not refute it. No details are provided about the methods of these studies, therefore it was not possible to evaluate their validity.
The review reports that “essentially no studies have compared the toxicity of silicofluorides with that of sodium fluoride, based on the assumption that the silicofluorides will have dissociated to free fluoride before consumption”. They report more advanced chemical studies looking at what happens to silicofluorides in water and suggest that “in drinking water of approximately neutral pH and typical fluoride concentrations all of the silicofluoride appears to be dissociated entirely to silicic acid, fluoride ion, and HF [hydrogen fluoride]”. One study author also suggested that the level of silica from the fluoridating agent is usually “trivial” compared to the natural levels of silica in water, and that any fluoridating agent or natural fluoride could give rise to the hexafluorosilicate ion if the correct conditions were present. The review suggests that further research is carried out to look at the properties of the fluoride and various fluoride compounds in water under different conditions.

This chapter did not aim to specifically review the safety of artificial fluoridation, and may not have identified all evidence relevant to this question.
Chapter 3: Pharmacokinetics of fluoride

Key message
This chapter describes studies in animals and humans looking at the pharmacokinetics of fluoride. In general, there is not much data on bone accumulation of fluoride with chronic low dose exposures in drinking water in humans. Estimates are calculated for lifelong exposure to drinking water containing 4mg/L and 2mg/L fluoride, but not 1mg/L. These should be considered relatively rough estimates, as they are based on pharmacokinetic models and few data.

The other important thing to note from this chapter is the differences between species in the pharmacokinetics of fluoride. These findings show the importance of considering results in animals as hypothesis generating, and requiring confirmation in human studies.

In addition they describe potential differences between long term low dose exposures (as in drinking water exposure) and short term high dose exposures to fluoride (as in therapeutics studies). This highlights the difficulties in extrapolating from therapeutic studies to what would be expected with drinking water exposure.

Summary of ‘Findings’
The chapter concluded that:

- Bone fluoride levels increase with both increasing dose and length of exposure to fluoride. Experimental data suggests that there can be substantial variations in bone fluoride levels for any set level of water fluoride.

- The best estimate of the level of bone accumulation of fluoride from a lifetime exposure to 4mg/L drinking water fluoride is 10,000 to 12,000mg/kg bone ash. This estimate is based on pharmacokinetic models, and would be higher in people with higher water intakes (over 2L a day) or with other sources of fluoride exposure. Estimated bone accumulation of fluoride from a lifetime exposure to 2mg/L drinking water fluoride is 4,000 to 5,000mg/kg bone ash; however, less data was available on which to base this calculation.

- The elderly and those with renal insufficiency are among the groups of people likely to have higher concentrations of fluoride in the bone.

- Pharmacokinetics should be taken into account when making inter-species comparisons of the effect of fluoride. Limited evidence suggests that rats need higher long term exposure than humans to achieve the same bone and plasma fluoride concentrations.

Bazian’s critique of this chapter (validity and applicability)
The review presents chemical information about fluoride, the forms it takes in the body, and how it is absorbed, distributed and eliminated from the body. The details of all of the studies referenced are not provided, but studies in animals are described, along with studies in humans (mainly cross sectional).

The chapter reports that few studies have been carried out that have compared bone concentrations of fluoride with chronic low dose consumption of fluoride in drinking water. Most of the studies are reported to be cross sectional and do not adequately assess length of exposure. Most of the data has come from autopsies. Studies on bone fluoride in people who have died may not accurately represent levels in the population, as those who have died at younger ages are more likely to have had health...
problems than the surviving population. In addition, it may be difficult to accurately assess exposure to fluoride in people who have died, as such information would need to be estimated based on records of residency areas, or to be provided by an informant such as a family member. The only study to include information on exposure durations was published in 1958, and exposure was assumed based on water concentrations of fluoride and assumptions about intake. This study included only 69 people, of whom 63 (aged 26 to 90 years) died suddenly from cardiovascular or cerebrovascular causes or trauma (three had kidney disease).

The chapter describes two new pharmacokinetic models of fluoride. The more complex of the models takes into account a variety of factors and can be used for predicting lifetime exposure. The data used to develop these models is not reported or assessed, although it was reported that the models performed well compared with study data from at least one human study and two animal studies. The reliability of the models will be based on their underlying assumptions, but these could not be evaluated.

In order to estimate the level of fluoride in bone with lifetime (70 year) exposure to water with 4mg/L fluoride in drinking water and in the absence of appropriate study data, the chapter authors used data from the more complex of the pharmacokinetic models. The accuracy of this estimate relies on the accuracy of the data and assumptions underlying the model. The authors report that the levels of bone fluoride calculated for 70 year exposure to water with 4mg/L (10,000 to 12,000mg/kg bone ash) lie outside the range of data used to build the model, which may affect the accuracy of this estimate.

Estimates for the level of fluoride in bone with lifetime (70 year) exposure to water with 2mg/L fluoride in drinking water from pharmacokinetic models had not been published, therefore the chapter authors used published data from three cross sectional studies from England and Finland in which bone fluoride concentrations were measured in people exposed to drinking water containing levels near to 2mg/L. They also used a regression model they developed using the data from the key study of bone fluoride levels from 1958 described above. These estimates are based on a relatively small amount of data, and should be considered rough estimates.

No estimates of bone fluoride concentrations with lifetime exposures of 1mg/L were given.

The chapter authors plotted the results from eight clinical studies of fluoride and compared this with estimates from the less complex of the fluoride pharmacokinetic models, and concluded that short term high dose exposures may produce higher bone fluoride than long term low dose exposures. This suggests that it may not be valid to extrapolate from therapeutic studies to chronic exposure at low doses, particularly for bone effects.

The chapter authors discuss interspecies differences in fluoride pharmacokinetics, which is an important consideration when extrapolating results from one species to the other. They say that most studies have been short term studies in mammals.

One review concluded that dogs were the best model for humans, as rats have three times larger renal and extrarenal clearance than humans. The methods of the studies underlying these conclusions were not reported. They also report that rat bone biology differs from that in humans and suggest that this will affect fluoride uptake by rat bones, which should be negligible in adulthood. They also note a number of other factors that can affect inter-species and comparison between different experiments in the same species. These include concentration of calcium in the diet (which can
affect fluoride uptake), concentration of fluoride in water and diet, level of food and water consumption, and rates of ageing in different species.

The chapter authors say that for rats, higher chronic exposures are needed to achieve the same plasma and bone fluoride concentrations as humans. The animal and human studies underlying this statement are described further in an Appendix. The exact conversion factors between rats and humans are reported as uncertain. These findings highlight the importance of interspecies differences, supporting the argument that animal data should be used as hypothesis generating, and human data on the effects of fluoride exposure should be used where possible.

The review also discusses factors affecting the pharmacokinetics of fluoride, and how these affect susceptible populations. The majority of the data reported pertained to people with kidney disease.

The data presented of this chapter is not directly relevant to the South Central SHA policy decision.
Chapter 4: Effects of fluoride on teeth

Key message
The chapter looked at the prevalence of severe fluorosis at different levels of drinking water fluoride, as well as the aesthetic and psychological effects of enamel fluorosis. It also looked at the potential for other dental adverse effects from fluoride. There were a large number of human studies cited in this chapter, mainly concerning the prevalence of severe enamel fluorosis. There were few human studies about the aesthetic and psychological effects of enamel fluorosis, or about other dental adverse effects from fluoride.

One key conclusion of this chapter is the recommendation by the committee that severe enamel fluorosis should be considered an adverse health effect. This decision was based on a majority vote, and was based largely on consensus in the dental literature and the fact that the condition is treated in dental practice, rather any new evidence about the condition’s health effects. This recommendation has important implications because the EPA needs to set the MCLG at a level that protects against adverse health effects, but not necessarily at a level that prevents adverse cosmetic effects. Up to the time of publication of this book enamel fluorosis was classed as a cosmetic effect by the EPA.

This chapter did not consider the dental benefits of fluoride, although they say that “many reports have discussed the inverse relationship between dental caries and water fluoride at concentrations considerably lower than the current MCLG of 4mg/L and SMCL of 2mg/L”

Although the chapter largely focuses on water containing 2 to 4 mg/L fluoride, some findings may be relevant to Southampton. For example, US studies found that the incidence of severe enamel fluorosis was close to zero at water fluoride level of below 2mg/L, and the proposed level of fluoridation in the South Central SHA (1mg/L) falls under this level. A large amount of evidence from human studies underlies the prevalence estimates, including studies identified in the York systematic review.

Summary of ‘Findings’
The chapter concludes that:

- Previous assessments considered fluorosis of any severity to be cosmetic, because there was a lack of evidence linking it to tooth loss, loss of function, or psychological, social or behavioural problems.
- However, the majority of the committee (ten out of twelve members) felt that severe enamel fluorosis should now be considered an adverse health effect. This is because severe enamel fluorosis involves loss of enamel (pitting) and structural damage to the tooth, which could lead to functional damage.
- There is little evidence about the effects of psychological, behavioural and social effects of enamel fluorosis.
- All members of the committee agreed that the MCLG should be set to prevent severe enamel fluorosis. This is in agreement with conclusions from the US Institute of Medicine, which have also been endorsed by the American Dental Association.
- Severe enamel fluorosis occurs in about 10% of children who are exposed to drinking water containing 4mg/L (the EPA’s MCLG). Therefore the MCLG does not protect adequately against this condition.
- Strong evidence supports a threshold effect in the US, with levels of severe fluorosis nearly zero at water concentrations of less than 2mg/L. There is no strong and consistent evidence
that by reducing fluoride levels from 4mg/L to 2mg/L would lead to a significant increase in the risk of caries.

- They suggest that the SMCL should be based on the discoloration of tooth surfaces, rather than its current basis on objectionable enamel fluorosis, which includes discoloration and/or pitting.

**Bazian’s critique of this chapter (validity and applicability)**

The authors note that they did not review evidence about whether drinking water fluoride protects against dental caries at levels less than 2mg/L. The parts of the chapter most relevant to Southampton are those looking at the prevalence of severe fluorosis at different concentrations of fluoride.

The chapter provides mechanistic information about the effects of fluoride on the teeth, as well as information from a few animal studies. The majority of information presented was from human studies which we have taken as providing the most valid evidence.

One key discussion in this chapter involved whether severe dental fluorosis was an adverse cosmetic or adverse health effect. Severe dental fluorosis had been considered an adverse cosmetic effect at the setting of the EPA’s guideline levels. However, if it is reclassified as an adverse health effect, the MCLG may have to be revised, as it should be set to ensure minimal adverse health effects.

Although no specific new studies regarding whether severe enamel fluorosis was an adverse health effect or an adverse cosmetic health were identified, the committee recommended that severe enamel fluorosis should be considered an adverse health effect rather than an adverse cosmetic effect. This decision appeared to be based on the general consensus in the dental literature about the adverse dental effects of severe enamel fluorosis, and the fact that the condition is treated by dentists to prevent further damage to the enamel and for cosmetic reasons. The majority of the committee agreed with this decision (10 out of 12 members). The other two committee members felt that severe enamel fluorosis was an adverse dental effect, but that no new evidence from the US had suggested that it might affect a person’s ability to function. Despite this, all members of the committee agreed that the MCLG should be set so as to prevent severe enamel fluorosis.

The chapter looked at the prevalence of severe fluorosis at different concentrations of drinking water fluoride, to see what threshold level was associated with minimal prevalence of severe fluorosis.

**Prevalence of severe dental fluorosis**

The NRC obtained international prevalence estimates from the EPA’s documentation supporting the MCLG, and from a systematic review published in 2000 from the University of York, the NRC identified an additional 24 studies. A systematic search strategy was not reported, but the chapter did report a set of inclusion criteria for studies, which aimed to ensure reasonable consistency between studies in methods of classifying dental fluorosis, and in methods of working out the prevalence of fluorosis.

The authors of the chapter cite examples of studies that they excluded based on each of the criteria given. Formal statistical analyses were not carried out because of the large variation in methods and populations, and results were plotted to look for general trends and patterns. These decisions appeared appropriate give the differences in the underlying studies.

The results found that the 94 US studies, despite methodological differences, showed a clear trend, with prevalence of severe fluorosis “virtually” zero in communities with less than 2mg/L fluoride in
their drinking water, and rising sharply in those with concentrations above 2mg/L. They say that this pattern differs from the linear trend seen when all levels of fluorosis are combined and plotted against either water concentration of fluoride, or daily dose of fluoride in milligram per kilogram of body weight, and provide two references for this observation. Results for 143 studies in children and adolescents from outside of the US were also plotted. Although these studies did show a positive link between severe fluorosis and level of fluoride in drinking water, the trend was less obvious, with no obvious threshold below which prevalence was very low. This may be because of the heterogeneity of settings. In general it seems likely that the UK would be more similar to the US in terms of lifestyle, diet, socioeconomic status, standards of dental and healthcare, education, and culture than to the non-US countries (including India, Sweden, Turkey, Brazil, Mexico, Ethiopia, South Africa, Uganda, Tanzania, Saudi Arabia and other countries). In the absence of specific UK data, the findings from the US may provide an estimation of what might be seen in the UK. Based on this, severe fluorosis is likely to be rare at the level of water fluoridation proposed for Southampton (1mg/L).

The review asks the question “Can the most severe forms of fluorosis (involving confluent dental pitting) occur at a concentration of 4mg/L?” as this is the existing MCLG level in the US. They identified three studies that reported severe enamel fluorosis with confluent pitting at levels of drinking water at or near 4mg/L, including among children. They say that reducing drinking water fluoride to less than 2mg/L would be expected to make severe enamel fluorosis very rare in the US, but not eliminate it completely.

**Aesthetic and psychological impact of fluorosis**

There was little evidence about the aesthetic and psychological effects of enamel fluorosis. One study from the US reported that parental satisfaction with children’s tooth appearance decreased as fluorosis increased. Although studies from some other countries supported this observation, others did not. One review looked at five studies and estimated that about 2% of schoolchildren who had fluoride exposure of 0.7 to 1.2mg/L might feel that they had aesthetic problems. However, it was noted that perceived aesthetic problems also occur in the absence of fluorosis, with one study finding that between 18 and 41% of people without fluorosis reported that they were not happy with the appearance of their teeth.

The 2000 York systematic review estimated that 63% of the population in the UK were likely to have enamel fluorosis of aesthetic concern at 4mg/L fluoride, 25% at 2mg/L, 15% at 1.2mg/L, and 6% at 0.1mg/L. The difference between 1.2mg/L and lower concentrations was reported to be not significantly different. However, the authors of the book note that this calculation was based on a single study from the UK. They say that these are likely to be overestimates, as they did not take into account the fact that some fluorosis occurred on the less visible back teeth, and that some children in the study in question found teeth with mild fluorosis more aesthetically acceptable than normal teeth. These seem reasonable observations, although we did not assess the validity of the York model or the underlying study. There are difficulties in diagnosis and classification of fluorosis, which are discussed in the chapter and there seems to be little consensus on how “aesthetic concern” should be defined and diagnosed. Because of these difficulties, and because these estimates are reportedly based on a single study they should be taken as rough estimates.

The book reported that no studies have quantified the prevalence of moderate fluorosis of aesthetic concern in the US. As studies have estimated that the prevalence of moderate fluorosis itself in the US as between 4% and 15%, the rate of moderate enamel fluorosis of aesthetic concern was estimated to be less than 15%.
Only one study assessed the impact of dental fluorosis on behavioural and psychological outcomes in children, and found no significant association between internalising and externalising behaviours and degree of fluorosis.

Dental caries and fluorosis
This chapter says that “many reports have discussed the inverse relationship between dental caries and water fluoride at concentrations considerably lower than the current MCLG of 4mg/L and SMCL of 2mg/L”, but these studies are not presented. The chapter presents seven studies in children in the US looking at the rate of dental caries in children exposed to levels of fluoride of 2mg/L and higher. These studies include groups of children exposed to 1mg/L fluoride, but there are no lower concentrations for comparison, so these data are not relevant to Southampton. No statistical comparison was given for the different concentrations of fluoride, but the evidence did not show a clear trend of increasing numbers of decayed missing and filled teeth surfaces from 1mg/L up to 5-7mg/L. Evidence from studies in other countries is also said to be unconvincing. The authors looked at the rate of dental caries among children with severe dental fluorosis and those with mild to moderate fluorosis in the same community, in order to gain an estimate the effect of reducing fluoride from 4mg/L to 2mg/L. Thirteen studies are described, and the evidence was mixed but generally supportive of an increased risk of dental caries in those with severe enamel fluorosis. These studies are reported to have a number of limitations; the main one is that there was no adjustment for dental care or oral hygiene. Other limitations include the lack of statistical comparisons, the fact that they were in widely varied settings (e.g. US, Africa, Turkey, Israel), and their cross sectional design.

As the concentrations of fluoride proposed for use in Southampton are 1mg/L, and at this level the rate of severe enamel fluorosis is predicted to be very low, the findings of these studies are not directly relevant to the South Central SHA policy decision.

Other effects
The authors discuss the rationale behind other potential dental effects of high fluoride, including an effect on dentin (dentine in UK English) for example, the increased risk of dentine fracture, or delaying the eruption of permanent teeth. They cite studies of the biology of dentine that support the hypothesis, and literature that have raised questions about tooth eruption, although the nature of these studies is not reported. This information is not sufficient basis for drawing a conclusion about these effects.

This chapter did not state whether the studies included only those of naturally fluoridated drinking water, or whether some looked at the effects of artificially fluoridated water.
Chapter 5: Musculoskeletal effects

Key message
This chapter looked at the effects of fluoride on bone as well as cartilage. There were a large number of human studies, particularly looking at fracture risk. This included observational studies of fluoride exposure, as well as randomised controlled trials of therapeutic fluoride exposure in people with osteoporosis.

The key message from this chapter is the committee’s recommendation that stage II fluorosis be considered the stage at which skeletal fluorosis becomes an adverse health effect. Previously only the more severe stage III skeletal fluorosis was considered to be an adverse health effect. As the MCLG aims to prevent adverse health effects, this redefinition may require a reconsideration of the MCLG. Stage III skeletal fluorosis is rare in the US, and there are no clearly documented cases of stage II fluorosis. In our opinion the evidence that stage II fluorosis can occur at the levels seen in the US was unconvincing.

The chapter concludes that lifetime exposures of 4mg/L or higher are likely to increase fracture risk, this conclusion was not unanimous among the committee. Results were inconclusive for 2mg/L. These results are not directly applicable to Southampton, where levels of 1mg/L are proposed. However, the book identified a 2000 systematic review from the University of York, which looked at the effects of artificial fluoridation on fracture risk, with particular emphasis on levels of exposure at or near 1mg/L. Although the NRC did not consider this systematic review, it is directly relevant to Southampton. It found no significant increase in the risk of fracture with levels of fluoride in drinking water at or near 1mg/L. As this review is systematic, its results are likely to be robust, and applicable to Southampton.

Summary of ‘Findings’
The authors’ conclusions include:

- Fluoride stimulates proliferation of the precursors of bone cells (osteoblasts) both in vitro and in vivo.
- Lifetime exposure to 4mg/L fluoride (the EPA MCLG) may induce stage II or III skeletal fluorosis and may increase the risk of fracture.
- The MCLG was set to protect against “crippling” skeletal fluorosis (stage III), however, the committee judged that stage II skeletal fluorosis should also be considered an adverse health effect, as it is associated with problems such as chronic joint pain and arthritic symptoms.
- The levels of fluoride in bone that result from a lifetime exposure to either 2mg/L or 4mg/L drinking water fluoride are estimated to be within or above the levels that have historically been associated with stage II and III skeletal fluorosis. Therefore, levels of 2mg/L or 4mg/L may not protect all of the population against these adverse health effects. However, this evidence is not conclusive proof that exposure to these levels of fluoride can lead to stage II skeletal fluorosis. There is little evidence about how common stage II fluorosis is in the US, and stage III fluorosis appears to be rare. More research is needed to study the relationship between fluoride exposure and skeletal fluorosis.
- Evidence from ecological (population level) exposure studies have consistently suggested that there is potential for increased fracture risk with 4mg/L in drinking water; only a few epidemiological (individual level) exposure studies were useful in addressing this question. Data from randomised controlled trials, animal studies, biochemical and physiological studies were consistent with the observational studies.
- All members of the committee agreed that there is scientific evidence that fluoride can weaken bone and increase risk of fractures under certain conditions.
- Most of the committee (9 out of 12 members) concluded that exposure to ≥4mg/L fluoride in drinking water over a lifetime is likely to increase fracture risk compared with lifetime exposure to 1mg/L fluoride in drinking water. This is particularly the case in subgroups of people more susceptible to fluoride accumulation in bone. The three remaining members though that the evidence only suggested the existing MCLG level of 4mg/L might not be protective against fracture. They felt that more studies showing an effect would be needed before concluding that the MCLG was likely to not be protective.
- Few studies assessed fracture risk in people exposed to 2mg/L fluoride in drinking water, and the committee judged that they could not draw firm conclusions on this issue based on the available evidence.

Bazian’s critique of this chapter (validity and applicability)

The chapter includes mechanistic information about the chemistry of fluoride, particularly in relation to bone, as the majority of the body’s fluoride is found in bone. The authors also report the effects of fluoride on bone cell function. Few details are given about the studies supporting these discussions. Most of this information appears to come from laboratory and animal studies. Chemically, fluoride is known to be incorporated into hydroxypatite crystals (the mineral component of bones) and also binds to their surface. In vitro and in vivo studies have suggested that fluoride can stimulate division of bone making cells (osteoblasts).

This mechanistic information provides a rationale for looking at the effects of fluoride on bone and for predicting what these might be, but cannot by itself prove that these effects will occur. The chapter also described studies in animals looking at the effects of fluoride on bone strength and fracture risk. However, inter-species differences (particularly between rats and humans) mean that these results should be interpreted cautiously, and that studies in humans are preferable sources of information.

The chapter illustrates the danger of extrapolating from mechanistic pathophysiological studies to clinical outcomes when describing the research conducted into whether fluoride could reduce osteoporotic fractures. Because of the effects of fluoride on bone cells, it was thought that it might be able to increase osteoblast numbers and therefore also increase bone production and reduce fractures in people with osteoporosis. The chapter reports that “hundreds” of reports of clinical trials were published, and although sodium fluoride (generally at doses of 30mg/day) was found to increase bone mineral density (BMD), it was not proven to reduce fractures.

Bone fracture epidemiology data

The chapter looked at human clinical trials and observational studies relevant to fracture risk at 2mg/L and 4mg/L fluoride in drinking water. The authors tabulated 26 observational studies (mostly ecological, but with some cohort and case control studies) looking at the effects of fluoride on fracture risk. They report that most of these studies have compared fracture risk in fluoridated (1mg/L) areas with that in non-fluoridated areas.

They report a 2000 systematic review and meta analysis by the University of York which specifically looked at the effects of water fluoridation at 1mg/L, and excluded data for areas with concentrations above this where data for 1mg/L were available. They found no significant difference in fractures between fluoridated and non fluoridated areas, but with significant heterogeneity in the analysis. No further appraisal of the quality of this meta analysis or most of the included studies was carried out in

Page 23 of 49
this book, as it did not fit the remit of their question, which pertained to the effects of 2 to 4mg/L fluoride.

However, this analysis and the systematic review from York is directly relevant to the South Central SHA decision. It asked the question “What are the positive and negative effects of population wide drinking water fluoridation strategies to prevent caries?” and it did this in a systematic way, meaning that its results are valid. This systematic review should be referred to for further discussion of the quality of the evidence regarding any association between fluoride and bone fractures (and other outcomes), and for the conclusions that the York reviewers draw from their assessment of these studies.

There were five observational studies described in detail in the NRC book that were not in the York systematic review. These included one study that correlated levels of fluoride in toenail clippings with fracture risk. It is not possible to determine level of exposure to drinking water fluoride from this study, and therefore it is does not provide directly applicable evidence for Southampton. One prospective cohort study from the US found a non-significant increase in risk of osteoporotic fractures in women with drinking water with 4mg/L fluoride compared with 1mg/L. One ecologic study from Mexico found an increase in risk of fractures with fluoride concentrations of 1.5mg/L to 4mg/L. An ecological study from Italy found an increased risk of fractures in a community with lower natural fluoride levels (0.05mg/L) than one with higher levels (1.45mg/L). A before and after ecological study from the US found a reduction in hip fracture incidence in people aged 50 years and over after the introduction of fluoridation (1.1mg/L).

As with all of the other studies, these studies have limitations to their designs, mainly the problem of confounding. The prospective cohort study had the most robust of the study designs used (although still subject to confounding), but the fluoride concentration assessed (4mg/L) in this study was higher than that proposed for use in Southampton, and therefore results are not directly applicable.

The NRC book discussed six observational studies looking at fracture risk with drinking water fluoride at levels of 4mg/L (or close to this concentation), and four observational studies with drinking water at around 2mg/L fluoride. In addition they also looked at a meta analysis of clinical trials of sodium fluoride treatment for postmenopausal osteoporosis in their consideration of the effects of 4mg/L. Their rationale behind this was that although the daily dose of fluoride (20 to 34mg) used in these trials was higher than would be received by people exposed to drinking water at 4mg/L fluoride, those exposed to such drinking water for a lifetime would have a similar if not higher cumulative exposure.

Although RCTs represent high quality evidence about the effects of the exposures tested, the results of these studies may not be applicable to the chronic ingestion of water in the general population, as they used a population already susceptible to fractures because of osteoporosis. In addition, acute high dose exposure and chronic low dose exposure may differ in their effects, and evidence presented in the pharmacokinetics chapter of the book (Chapter 3) gives some indication that this might be the case with bone accumulation of fluoride. The results of these RCTs are not applicable to Southampton.

The observational studies showed evidence of an increased fracture risk with fluoride at 4mg/L, although this increase was not statistically significant in all studies. The meta analysis showed a significant increase in risk of new non-vertebral fractures with 4 years’ sodium fluoride treatment (the increase was not significant at 2 years), but no significant difference in risk of new vertebral
fractures (in fact there was a trend towards a decrease). Findings of the observational studies looking at exposures of 2mg/L were mixed.

The committee judged that the evidence about exposures of 2mg/L were inconclusive, but that lifetime exposures at 4mg/L and higher were likely to increase fracture rates in the population compared with exposure at 1mg/L. This conclusion was based on the “weight-of-evidence” approach and included an assessment of consistency of findings of the observational studies, the strength of the association, biological plausibility and coherence (evidence from biochemical, physiological, and animal data, with support from RCT evidence), and evidence of dose response from the observational studies. It should be noted that three of the twelve committee members thought that exposures of 4mg/L might be likely (rather than were likely) to increase fracture risk and that further human studies were needed. This illustrates that fact that there were some differences in how the evidence was interpreted.

**Skeletal fluorosis**

The committee first discussed what level of severity of skeletal fluorosis should qualify as an “adverse health effect”. In setting the existing MCLG, the EPA only considered “crippling” (stage III) skeletal fluorosis, and therefore the MCLG was set to avoid this effect. The committee thought that stage II skeletal fluorosis should be considered the first stage at which the condition was an “adverse health effect” because it affected mobility and was a precursor to more serious mobility problems (stage III fluorosis). This judgement by the committee appeared to be made based on their expert knowledge about the effects of stage II skeletal fluorosis, as no direct evidence was presented about quality of life or levels of disability associated with the different levels of skeletal fluorosis. If this recommendation was accepted by the EPA, the MCLG would need to be reviewed and adjusted as necessary to reduce the likelihood of this effect in the population.

The committee then considered the evidence about whether stage II skeletal fluorosis was present in the US, and at what levels of fluoride exposure it exists. One study was only able to find five reported cases of stage III skeletal fluorosis in the US between 1960 and 1997. No studies clearly reporting stage II skeletal fluorosis in the US, or looking at the prevalence of stage II fluorosis at different levels of exposure to fluoride were reported. Instead the book compared the levels of fluoride in bone that have historically been associated with different stages of skeletal fluorosis, and compared this with the estimated bone accumulation of fluoride from a lifetime exposure to 4mg/L drinking water fluoride. This estimate was calculated in the pharmacokinetic chapter of the book (Chapter 3) based on a pharmacokinetic model and few data.

These calculations should be seen as hypothetical. The studies looking at fluoride concentrations in bone included were very small, with very few individuals at each stage (ranging from 1 to 18 people), ranges of bone fluoride for each stage were found to be wide and overlap, and differing methods for fluoride measurement were used, and in different bones. This method also cannot determine how likely skeletal fluorosis is at these bone fluoride concentrations, or at different levels of exposure.

As no clear cut reports of stage II skeletal fluorosis were found it is not possible to report what levels of stage II skeletal fluorosis might be associated with different levels of exposure.

The fact that so few reports of stage III skeletal fluorosis and no clear reports of stage II fluorosis were identified for the US, where higher fluoride concentrations are allowed than in the UK, suggests that stages II and III skeletal fluorosis are likely to be even less common in the UK.
**Chondrocyte metabolism and arthritis**

Little information was available about the effects of fluoride on chondrocytes, but overall the authors reported that there was likely to be no effect of fluoride at environmental doses, and a small effect at therapeutic doses (e.g. the doses as tested for osteoporosis).

The studies presented included a case report looking at fluoride levels in the calcified hip joint cartilage of a woman treated with fluoride for osteoporosis, however, the calcification seen may have occurred before starting treatment. Two other studies looking at the effects of fluoride at therapeutic doses in people with rheumatoid arthritis were described, but they found conflicting results. Neither of these studies is relevant to the consideration of the effects of chronic ingestion of fluoride in drinking water. One study from Turkey compared patients with fluorosis with age and sex matched controls for osteoarthritis symptoms and osteophyte presence. No description of the level of these people’s fluoride exposure is given. Results in people with fluorosis are not likely to be representative of what would be seen in the general population.

A few studies in animals and in vitro studies are described, but these may not be representative what would happen in humans.
Chapter 6: Reproductive and developmental biology

Key message
The study included studies in animals which suggested that fluoride only has reproductive and developmental effects at high concentrations. There were few human studies on the effects on reproduction. Those that existed had methodological weaknesses and looked mainly at proxy outcomes rather than clinical outcomes such as fertility. The only study looking at fertility had methodological weaknesses and looked at concentrations of fluoride of higher than 1mg/L, therefore it is not directly applicable to Southampton.

There were similar concerns about the studies on developmental effects, although some studies did look at clinical outcomes such as spina bifida, Down’s syndrome, and sudden infant death syndrome. These studies did not provide any convincing evidence of developmental harms with fluoride exposure from drinking water. The studies of SIDS and found no increase in the risk of SIDS with artificially fluoridated water at around 1mg/L in New Zealand, and are likely to be applicable to the Southampton setting.

Reproductive and developmental toxicity were not toxicities that contributed to the committee’s decision to recommend lowering the MCLG.

Summary of ‘Findings’
The authors conclude that many studies of the effects of fluoride on animal reproductive and developmental biology have been published since 1990. High quality studies in animals of between 0 and 250mg/L fluoride in drinking water have found that adverse effects occur only at very high concentrations. Findings of some human studies have suggested that fluoride might affect reproductive hormones, fertility and be associated with Down’s syndrome. However, these studies have design limitations which mean that they are not useful for risk evaluation.

Bazian’s critique of this chapter (validity and applicability)
These conclusions are appropriately cautious given the strength of the evidence on which they are based. Methods of the chapter are not reported, although the authors say that a search of the literature was carried out. No details of this search are provided nor are there details of the inclusion and exclusion criteria. It was not clear whether all studies which were identified were discussed, or simply those that were illustrative of the body of evidence.

Reproductive effects
A large number of animal studies in a range of species were presented (rats, mice, rabbits, guinea pigs, sheepdogs, and frogs). These studies almost all used sodium fluoride, and this was given in large doses ranging from 5mg/kg/day to 48mg/kg/day (force fed or by injection) or 10mg/L to 600mg/L in drinking water, and frog embryos were incubated in water containing 100 to 1000mg/L. These studies are appropriate for identifying the potential hazards that fluoride may have in humans, but because or inter species differences and the high doses used may not be representative of what would be seen with chronic exposures in humans at lower doses.

The authors themselves report that there were few human reproductive studies (8 are described), and that they suffer from design and power limitations and problems such as confounding.
For those studies where the level of fluoride in drinking water was quantified, it was greater than 1mg/L. Only one of the studies described actually looked at the effect of fluoride exposure on a clinical outcome - fertility rate. This study compared fertility rates in regions of the US with different levels of drinking water fluoride (≥3mg/L) and found an association between the two. However, this study is subject to confounding, and the review authors acknowledge that there may not have been adequate control for potential confounders such as the use of contraception and family income.

Four of the remaining studies listed looked at the level of fluoride in the cord blood, amniotic fluid, or neonatal blood in women exposed to drinking water fluoride. These findings do not necessarily indicate any harm to mother or baby. One of these studies also exposed male sperm to different levels of sodium fluoride in vitro and looked at various proxy outcomes including sperm motility. However, as this was an in vitro study, and it is not clear whether similar outcomes would be seen in vivo men who drink water containing fluoridate. Two further studies looked at proxy outcomes, such as level of testosterone and semen characteristics, rather than the clinical reproductive outcome of fertility rate. It is not possible to extrapolate from these proxy measures to say whether there would be an effect on fertility.

**Developmental outcomes**

Of the studies looking at developmental outcomes, several were reported to look at outcomes such as level of fluoride in the amniotic fluid of pregnant women exposed to drinking water containing fluoride, or in foetal bones, cord blood or blood from the baby. These studies confirm that fluoride is absorbed, but the outcomes do not necessarily indicate any harm to mother or baby. Other studies looked at the conditions spina bifida, Down’s syndrome, and sudden infant death syndrome.

One study from India looked at the rate of spina bifida occulta among children in areas with exposed to 4.5 to 8.5mg/L fluoride, but there did not appear to be any control group, meaning that no inferences could be drawn about the effects of fluoride. A similar study from India did compare children from high fluoride areas (4.5–8.5mg/L drinking water) with those from a low fluoride area (≤1.5mg/L drinking water). However, no information is provided about whether the groups were balanced for potential confounders, in particular folic acid intake among mothers, and this would be an important consideration in determining the reliability of the study. In addition to the reported methodological weaknesses of these studies, they are not directly applicable to Southampton because the concentrations of fluoride assessed are higher than those proposed for use in this area (1mg/L).

Some ecological studies are reported as looking at the prevalence of Down’s syndrome in communities with differing levels of fluoride in drinking water. The book authors report that these studies are difficult to analyse because the accuracy of case identification is in doubt as a variety of non-definitive sources were used (birth certificates, parents, hospital records). There was also a lack of information about individual mothers’ levels of exposure, and the studies were prone to the effect of the confounding factor of maternal age. One review of this literature is described, but it was not reported whether this review was systematic. This found mixed results from studies looking at communities with fluoride concentrations up to 2.8mg/L, and the studies were reported to be of poor validity.

Two studies from New Zealand looking at sudden infant death syndrome (SIDS) are reported. One study is reported to be based on data from a literature search, but whether this was a systematic review is not reported. It found that there was no significant association between SIDS and average fluoridation. The median fluoridation level was ≤1mg/L. Another nationwide case control study of 485 cases and 1,800 controls found that exposure to artificially fluoridated water (0.7mg/L to 1.0mg/L) in
uterine did not affect risk of SIDS. Fluoridated water did not increase risk of SIDS among breastfed infants, and fluoridated formula feeding did not increase risk of SIDS compared with unfluoridated feeding. These results would appear to be relevant to the South Central SHA decision because of the comparable levels of fluoridation, and the use of artificial fluoridation in at least one of the studies.
Chapter 7: Neurotoxicity and neurobehavioural effects

Key message
The authors’ main conclusion in this chapter is that more research is needed.

There were few studies in humans reported in the book. The few studies of the effects on IQ that are reported were carried out in China, and may have limited relevance to the UK because of differences in drinking water standards and socioeconomic and other factors. The association between IQ and fluoride levels in drinking water identified in these observational studies may be due to confounding and bias. In addition, levels of fluoride in drinking water in these studies (about 2.5 to 4mg/L) was higher than that proposed for use in Southampton (1mg/L), and therefore are not directly applicable to Southampton. [NB These and other studies of the effects of fluoride on IQ have been critically appraised by Bazian, please see accompanying report for further details.]

Evidence about effects on other outcomes, or of a difference in the effects of fluorosilicates used for water fluoridation and other fluoride compounds is sparse and inconclusive.

Neurotoxicity was not a toxicity that contributed to the committee’s decision to recommend lowering the MCLG.

Summary of ‘Findings’
The authors conclude that:

- They identified three observational studies of drinking water fluoride concentrations within the EPA’s SMCL and MCLG. These studies were carried out in China, and found that children in areas with fluoride concentrations of 2.5 to 4 mg/L had lower average IQ scores than those in areas with fluoride levels 0.4 to 1mg/L. The authors could not fully assess the quality of these studies or their relevance to the US as they lacked methodological detail. However, the consistency of the findings led the authors to suggest that further research was needed in this area.
- Some animal studies have suggested that fluoride can affect basic behaviours, but the changes seen were not large, and could have been due to reasons other than the fluoride treatment. No studies have assessed effects on more advanced mental function, or response to stress or disease.
- Fluorosilicates are the forms of fluoride used to fluoridate water. Some research suggests that they may increase uptake of lead into the body, whereas fluoride salts do not. More research is needed to determine whether these compounds differ in their effects from fluoride salts.
- Fluorides affect lipids, protein and enzymes in the brain of laboratory animals. More research is needed to investigate the effects of fluoride on brain biochemistry.
- Sodium and aluminium fluoride have been shown structural alterations to neurons in various areas of the brains of rats, and aluminium could be found in the neurons and other cells of the brain. The changes seen were large and consistent in different studies. Some of the changes seen in rodents are related to signs of dementia in humans. More research is needed in this area.

Bazian’s critique of this chapter (validity and applicability)
This chapter includes both human and animal studies, although mainly animal studies, as well as in vitro experiments.
A small number of Chinese studies found a reduction in IQ with high fluoride exposure from either drinking water or coal burning, but the studies had weaknesses in their designs that mean that their findings may not be reliable. The results of these studies are unlikely to be directly applicable to Southampton, as the levels of drinking water fluoride were above 1mg/L (the proposed level for water fluoridation in Southampton) and children in China may have also had considerable fluoride exposures from non-drinking water sources. There are likely to be other differences between China and the UK (such as general water quality and socioeconomic factors) that also limit the applicability of these studies.

Studies in animals showed inconsistent evidence of limited changes in behaviour. Due to interspecies differences these results are unlikely to be representative of what would be seen in humans. These studies generally used concentrations of fluoride in excess of the levels that humans would be exposed to from fluoridated drinking water, and mainly used fluoride salts (sodium and aluminium fluoride) rather than the fluorosilicates which are used to fluoridate drinking water.

**Cognitive effects**

The book cites four main Chinese studies, all of which were observational in their design (they appeared to be cross sectional). They compared children’s IQ in areas with higher fluoride exposures with areas with lower fluoride exposures. In three of these studies fluoride exposure from drinking water was estimated, but the fourth examined fluoride exposure from indoor coal fires. The higher fluoride drinking water areas had concentrations of fluoride ranging from 2.47 to 4.12mg/L and the low fluoride areas 0.36 to 0.91mg/L. In two of the studies the comparator groups were reported to be balanced or similar for some potential confounding factors such as educational levels, but there may have been other factors that may have been imbalanced between the groups. The other studies did not report whether groups were balanced.

All of the studies showed lower IQ in the high fluoride areas, but no statistical comparisons were presented in the book. Another study was mentioned that found a link between fluoride and IQ, but no further details of this study were provided. [NB These and other studies of the effects of fluoride on IQ have been critically appraised by Bazian, please see accompanying report for further details.]

The book notes that the significance of the findings of these studies is uncertain, and assessment of the strength of their findings was not possible, as most were brief reports with little methodological detail e.g. of the IQ tests used and how they were administered and whether assessors were blinded. However, they felt that the consistency of findings across these studies meant that further research on the effects of fluoride exposure on IQ was warranted.

These studies have methodological weaknesses. All of the studies were of observational design, and the groups may have differed in factors other than fluoride exposure, and that these differences could be responsible for the differences seen in IQ rather than fluoride (known as confounding). In addition, all of the studies appeared to be cross sectional, measuring IQ and assessing fluoride exposure at one point in time. Therefore it is not possible to say whether fluoride exposure preceded development of differences in IQ between the groups. Although some studies measured fluoride at an individual level by measuring fluoride in their urine, this was only carried out at one time point, therefore lifetime exposure to fluoride was unclear.

The studies looked at concentrations of drinking water fluoride higher than 1mg/L, or exposures from coal fires, and therefore these results are not directly applicable to Southampton. Other differences also limit the applicability of these findings. In particular, it is not clear how tightly water quality is
controlled in China compared to the UK. Areas where fluoride levels in drinking water are high may also have high levels of other water contaminants which confound findings. In addition, the use of high-fluoride forms of coal for heating and drying foodstuffs and consumption of high-fluoride forms of tea (brick tea) means that an individual’s fluoride exposure may be much higher than would be expected from assessing drinking water levels.

The authors say that there are “numerous reports of mental and physiological changes after exposure to fluoride from various routes (air, food, and water) and for various time periods”. They reference this statement with a book published in the 70’s but do not list these reports themselves. They say that they include blinded tests where symptoms were found to disappear when exposure was removed, and return on re-exposure, and also cases where symptoms appeared only when in individual moved into a fluoridated area and resolved once they moved out of the area. Well conducted blinded experiments may provide good quality evidence of an effect. However, not enough information is provided by the book to determine the reliability of these reports. In addition, no description of the symptoms experienced is given, so it is not possible to determine how serious these symptoms were. The studies of people moving into and out of fluoridated communities may be confounded by other conditions that differ between the two areas, or by the passage of time between living in the different communities.

They chapter also describes the findings of a review of case reports and surveys of people exposed to fluoride occupationally or therapeutically. Only 12 case reports are described in the book, and symptoms reported include lethargy, weakness, impaired ability to concentrate, and impaired memory in some cases. Case reports can only offer low level evidence about the effects of an exposure, as there is no control group, and it is difficult to attribute symptoms seen (which were relatively non-specific in these cases) to one particular cause. No indication of levels and routes of exposure to fluoride are given. In addition, these studies cannot give any indication of how common any particular symptoms are in the general community as there is no denominator for the number of people exposed, or systematic identification of people with particular symptoms. These findings are not convincing of an effect on mental function.

**Effects of silicofluorides**

The chapter authors discuss the possibility that silicofluorides, which are the compounds used in drinking water fluoridation, may have different biological effects to other fluoride salts. They say that adding sodium silicofluoride or fluorosilicic acid to drinking water has been reported to increase accumulation of lead in the body. They reference two studies for this statement, but do not discuss them in depth. They go on to discuss other researchers’ criticisms of these two studies, including measurement and statistical limitations, leading to these researchers’ conclusion that there was no credible evidence of an effect on lead in the body.

They also discuss a dissertation from 1975 and another study by the same author that found that silicofluorides inhibited the production of cholinesterases, the enzymes that break down chemicals such as the neurotransmitter acetylcholine, more than sodium fluoride. It was not clear whether these effects were observed in humans, animal or in vitro, although the tone of the discussion (about the effects at “physiological levels”) and the title of the dissertation suggest that they are likely to be in vitro. Studies in vitro may not accurately represent what happens in the body, and cannot determine whether any practical effects of changes would be seen.

The chapter authors cite a meeting abstract reporting non-cognitive impairments in children, but this study had not been published in full. This means that the study had not undergone the quality control
peer review process usually required for publication in a scientific journal. In addition, no details of what exposures these children had experienced or the extent of these impairments was given, and limited information about the study's methods were available on which to judge its quality.

The evidence provided is very limited and not conclusive.

**Dementia**

The chapter authors discuss mechanistic reasons why fluoride might have an effect on dementia, in particular its affinity for aluminium. However, mechanistic reasoning can only generate hypotheses and not prove an effect.

The book describes a study in France that showed an association between cognitive ability in older adults and calcium, aluminium and fluoride in drinking water. However, only aluminium showed an association with cognitive impairment, i.e. fluoride did not. Not enough methodological information was provided about this study to judge its quality, and it is unclear whether any other studies have looked at the relationship between fluoride and dementia and what they found. No information about the levels of fluoride or other chemicals in this study were provided.

The book reports that epidemiological studies have found inconsistent results; however, this statement appeared to refer to aluminium rather than fluoride. They also discuss animal and cellular research on the effects of aluminium, and on aluminium fluoride complexes. However, it is unclear to what extent these findings would apply to humans.

The links between fluoride and dementia discussed in this section are largely based on knowledge of the chemical properties of fluoride and its biochemical effects, rather than direct evidence of a link from epidemiological studies in humans. As such this link should be considered hypothetical rather than likely or proven.

**Animal studies**

The authors discuss behavioural, anatomical, and neurochemical changes in laboratory animals exposed to sodium fluoride and aluminium fluoride. They also discuss the effects of fluoride on various biochemicals, such as phospholipids, in the brains of animals, as well as in in vitro studies.

Findings in rats and mice or in vitro are not necessarily indicative of what would happen in humans. In particular, behaviour is a very complex characteristic, and extrapolations between animals and humans are particularly difficult. In addition, the studies mostly involved doses much higher than the levels proposed for use in Southampton. In addition, the aluminium in the aluminium fluoride used in some experiments compounds may itself have been having an effect rather than the fluoride.

The results obtained in these studies may not be representative of what would happen in humans.
Chapter 8: Effects on the endocrine system

Key message
This chapter looked at effects on a number of endocrine organs including the thyroid, parathyroid, pineal, adrenal, and pituitary glands, as well as the pancreas.

The evidence about effects of fluoride on the endocrine system comes largely from animal studies. Evidence from human studies of an adverse effect on the endocrine system is generally weak. As the authors of the book note, most of the evidence is about proxy outcomes and not about adverse health outcomes.

Endocrine toxicity was not one of the toxicities that contributed to the committee’s decision to recommend lowering the MCLG.

Summary of ‘Findings’
The review concluded that:

- The main effect of fluoride on the endocrine system in humans and animals was decreased thyroid function, increased calcitonin activity, increased parathyroid hormone activity, secondary hyperparathyroidism, impaired glucose tolerance, and possible effects on timing of sexual maturity.
- Some of these effects are seen at concentrations which are achievable by drinking water containing 4mg/L or less, particularly for young children or people with high water intake.
- Many of the effects could be considered subclinical rather than clinical (adverse health) effects. However, recent research has suggested that apparently mild hormonal disturbances may be associated with adverse health effects or increased risks of developing adverse health effects. Further research is needed to investigate these possibilities.

Bazian’s critique of the chapter (validity and applicability)
This chapter discusses the biology of the endocrine organs, what is known about the biology of fluoride in these organs, and mechanistic theories about how fluoride might affect the function of these organs. This information is helpful in understanding the rationale behind considering the effects of fluoride on endocrine function and in explaining an effect once it has been observed. However, mechanistic information cannot be used to prove an effect, for this evidence from human studies are needed.

The experiments in animals do not necessarily accurately reflect what would happen in humans because of inter-species differences. The review itself notes this to be the case, reporting that similar effects to those seen in rats or mice were seen in humans at lower fluoride intakes.

The chapter reported that the effects of fluoride on thyroid function (altered hormonal levels and goitre prevalence of 20% or higher) have typically been seen at daily fluoride intakes of 0.05 to 0.1mg/kg/day (or with 0.01 to 0.03mg/kg/day in people with iodine deficiency). Other endocrine effects (such as elevated calcitonin levels, impaired glucose tolerance in some individuals, increased parathyroid hormone concentrations, and secondary hyperparathyroidism in some individuals) have typically been seen with fluoride exposures ranging from 0.06 to 0.87mg/kg/day.
The chapter notes that the effects seen could occur at lower or higher exposures than those described. As most of the studies did not aim to identify the lowest or higher concentrations at which these effects occurred, this possibility will need to be confirmed in human studies.

The level of evidence supporting these ranges is weak. In particular, the key study reported as underlying the level of fluoride intake required for elevated calcitonin concentrations was a very small case-control study of 9 cases with moderate to severe skeletal fluorosis and 5 controls, and the lower limit of the range is based on just one of the cases. This study also seems to underlie the lower boundary of the range of fluoride exposures typically associated with increased parathyroid hormone concentrations. The results of this study clearly cannot be taken as indicative of the general population, and any estimation based on its results are unreliable.

Most of the reported effects of fluoride were not adverse health effects, rather proxy outcomes including changes in physiological parameters (such as hormone levels). In addition, in some cases, although different from the unexposed group, the review reported that average hormone levels in the exposed group were still in the normal range. Although it may be possible that the hormonal changes seen may be associated with adverse health effects, further human studies will be needed to confirm this.

From the results presented it appeared that alterations in endocrine function were not always consistent across studies. For goitre, not all of the studies found an association with fluoride, and this was also the case for studies of thyroid hormones and blood glucose measurements. Studies of parathyroid gland function were also reported to show different responses among individuals, and variability in group responses.

Neither of the two studies on age at menarche were reported to find any statistically significant differences in average menarche age between fluoridated (1.1 to 1.2mg/L) and non fluoridated areas (one are reported as “essentially fluoride free” and the other 0.2mg/L). One study found that girls in the high fluoride area were more likely to have reached menarche by age 15 than in the non-fluoridated area, but whether this difference was significant was not reported. These findings are not conclusive.

At 1mg/L fluoride, the level suggested for fluoridation in Southampton, the average adult would be exposed to about 0.03mg/kg/L, below the levels reported to be typically associated with the effects described. However, those with an iodine deficiency may be particularly susceptible to thyroid effects, and those with particularly high water intakes (e.g. because of a medical condition) might have higher exposures. However, the limitations of this evidence described above should be borne in mind, and the conclusions seen as tentative. In particular, for goitre, the study with levels most closely representing the proposed levels for the Southampton found no significant effect of fluoride. While another study from Nepal found a link at levels of fluoride less than 1mg/L, this setting may not be representative of the UK setting. In particular, the levels of iodine in drinking water was low (≤1μg/L), diets were low in iodine, and iodised salt was not available. In addition, sociodemographic differences between Nepal and the UK may also limit applicability. This study by itself cannot prove that the lack of fluoride directly increases risk of goitre, as although some population level confounders were taken into account individual confounders or residual population level confounding may be having an effect. The other studies that found an association between goitre and fluoride had levels of fluoride higher than 1mg/L, and therefore these are not likely to apply in Southampton.
In summary, most people exposed to drinking water fluoride at 1mg/L will not reach the levels of fluoride which have been reported in this chapter to be associated with endocrine system effects. The evidence underlying the ranges of fluoride dose in which endocrine effects typically occur is not strong, and should not be interpreted as levels at which endocrine changes will definitely happen. In addition, the effects seen were physiological changes, such as changes in hormone levels, rather than adverse health effects.
Chapter 9: Effects on the gastrointestinal, renal, hepatic, and immune systems

Key message
The level of evidence about the effects of fluoride on the gastrointestinal, renal, hepatic, and immune systems was generally low, mainly consisting of case reports in humans, plus a few ecological studies. None of these sources provide convincing evidence of harm with chronic ingestion of drinking water at 1mg/L, the level proposed for use in Southampton.

Gastrointestinal, renal, hepatic, and immune system toxicities were not toxicities that contributed to the committee’s decision to recommend lowering the MCLG.

Summary of “Findings”
This chapter concluded that:

- There were no human studies showing ‘careful documentation’ of gastrointestinal (GI), kidney, liver, or immune effects with drinking water at 4mg/L.
- Case reports in humans, studies in animals, and in vitro studies suggested that fluoride at concentrations higher than 4mg/L can be irritating to the GI system, affect liver and immune parameters, and affect kidney tissue and function. These effects are unlikely to be a risk for the average person exposed to fluoride at 4mg/L. However, people with kidney impairments who retain more fluoride than healthy individuals may be a potentially susceptible subpopulation.

Bazian’s critique of this chapter (validity and applicability)
This chapter discusses the biology of the organ systems assessed, what is known about the biology of fluoride in these systems, and mechanistic theories about how fluoride might affect the function of these organs. This information is helpful in understanding the rationale underlying the potential effects of fluoride, or explaining an effect once it has been observed. However, mechanistic information cannot be used to prove an effect, for this evidence from human studies are needed.

The chapter includes experiments in animals, and also studies on human cells in vitro. The experiments in animals, although helpful in determining of the types of toxicity and the organ systems affected by fluoride, do not necessarily accurately reflect what would happen in humans, because of inter-species differences. The experiments on human cells again are helpful in looking at potential effects, but may not be representative of what will happen in the same type of cells in the body when fluoridated water is consumed. This is because concentrations of the test chemical (in this case fluoride) and chemical composition and pH of the solutions in which the cells are grown in laboratory experiments may not replicate what would be seen under physiological conditions. In addition, cultures of single cell types in a petri dish, or single tissues cannot replicate the complex organ systems in which the cells operate in the body: interaction with other cell types, the structure of the tissue, and interaction with other systems in the body are likely to affect how cells respond to chemicals. Therefore, studies in humans provide the best available evidence for assessing toxic levels, and we have concentrated on this evidence, as this has the greatest bearing on the South Central SHA policy decision.

GI system
Studies included in the assessment of the effect of fluoride on the GI system were mainly case series consisting of people reporting effects on ingestion of fluoridated water at standard levels (1mg/L;
two case series including 72 people), acute ingestion of water over-fluoridated by accident (20 to 300mg/L; six case series), or over ingestion of fluoride containing products such as toothpaste or mouthwash (various concentrations; one case series). There were also the results of experimental studies, such as a double blind controlled study looking at the effects of water containing 1mg/L fluoride, an uncontrolled study of fluoride gel ingestion (3g of gel containing 4,200mg/L fluoride), a clinical trial of sodium fluoride supplements (1.2mg) in pregnant women and their children, and one of sodium fluoride (30mg/day) in people with otosclerosis.

The review found no studies that had “carefully assessed” the effects of drinking water containing 4mg/L fluoride on GI symptoms.

In terms of Southampton, only the studies looking at standard levels of water fluoridation would be directly applicable. Although the acute accidental ingestion studies provide robust evidence that GI symptoms can occur with high level fluoride exposure (about 50% to 90% if those exposed reported GI symptoms with exposures of 41 to 300mg/L), they are not likely to be illustrative of what would happen chronic ingestion of much lower levels of fluoride (1mg/L). Clinical trials assessing the effects of fluoride compounds for osteoporosis have also suggested that they are associated with GI symptoms, but again the acute concentrations of fluoride in the stomach would be higher than expected with fluoridated water ingestion, and therefore not applicable to this setting.

Of the relevant studies, one study from 1956 reported on 52 people who experienced GI symptoms such as stomach cramps, and abdominal pain when they drank artificially fluoridated water, and these symptoms resolved once they stopped drinking fluoridated water. Another from 1977 reported on 20 people who experienced GI symptoms such as stomach cramps, and abdominal pain when they drank artificially fluoridated water, these people also experienced other symptoms such as fatigue, skin itching (pruritis), headaches, and excessive thirst (polydipsia).

This type of study has a number of limitations. In particular, it is not possible to estimate the proportion of people in the population who experience this type of symptoms, and as the cases are sporadic it is difficult to be certain what caused the symptoms. Although one study reports that symptoms went away after stopping drinking fluoridated water, this could have been because symptoms were due to another cause (e.g. viral or bacterial infection), which had gotten better naturally by the time of the switch. These studies were carried out over 30 years ago, and it is unclear whether the chemicals and processes used for fluoridation at that point are the same as those currently used.

The double blind experimental study included 60 people from the Netherlands who reported GI symptoms with fluoridated water, which went away on stopping drinking the fluoridated water. They were given eight bottles of water containing either fluoridated water (sodium fluoride and Na₂SiF₆ to a fluoride ion concentration of 1mg/L) or distilled water. The review did not state whether the fluoride compounds were dissolved in distilled water to make the groups directly comparable. Participants were asked to use one bottle at a time for 2 weeks, and to record their symptoms. It found that half of participants had GI symptoms and 30% had stomatitis. It was not clearly stated whether these symptoms were specifically experienced during exposure to the fluoridated water, and if this was the case, what the rate of these events was when drinking the distilled water.

This study’s strengths include its use of a control exposure and its double blind nature. It is possible that people were able to taste the difference in the two samples, and therefore be unblinded; the chapter did not report whether the study assessed this possibility. As the authors suggest, it may not
be representative of the normal population as the study only included people who had already experienced GI symptoms with fluoridated water, and were possibly hypersensitive. As a single small study, its results ideally need confirmation by other studies.

**The renal system**

Three human studies were described that looked at bladder and kidney stones (urolithiasis), two ecological studies, and one case series. The case series looked at fluoride intake in 20 children with urolithiasis. As this study had no control group, it is not possible to tell whether the children’s fluoride intake differed from that of children without urolithiasis. An Indian ecological study looked at fluoride endemic (3.5 to 4.9mg/L) and non-endemic areas and found an increased rate of urolithiasis in the endemic areas. This study looked at concentrations near to the US MCLG, but the chapter authors report that this study was not likely to be representative of the US setting as malnutrition was likely to have increased the risk of kidney stones. The Swedish ecological study found mixed results in the two parts of its study. Areas with 1.5mg/L of higher having about a sixth more admissions with urolithiasis, but no differences were seen for lower fluoride areas (0.5 to 1.49mg/L or less than 0.5mg/L). The comparison group was not clearly reported for this part of the study. However, in a separate part of the study, a fluoridated city (1mg/L) was found to have 25% lower rates of urolithiasis than a non-fluoridated area (<0.49mg/L).

The results from the Swedish study appear relevant to Southampton, because of the similar concentrations of fluoride involved. However, the conflicting results from the different parts of the study suggest that the result should be seen as inconclusive, as some factor(s) other than fluoridation seems likely to be affecting the results.

The chapter discusses studies of the effects of fluoride on measures of kidney function. It should be noted that alterations in measures of kidney function do not necessarily mean that the individual will have any clinical adverse effects. The authors state that there are no published studies that show fluoride consumption at 0.014mg/kg/day (the level of exposure for a 70kg person drinking 1L of 1mg/L fluoridated water a day) can affect the kidney. They do cite various studies looking at renal function in patients exposed to fluorinated general anaesthetics. The effects of fluoride in these anaesthetic compounds may not be the same as that of fluoride in fluoridated water, as any effects seen could be due to the non-fluorine containing metabolites of these compounds rather than the fluoride. Also, the doses that would be involved give rise to higher serum fluoride levels than would be likely to be experienced with drinking fluoridated water at 1mg/L. As such this evidence is not likely to be directly applicable to chronic fluoride exposure from water in general, or to South Central SHA policy decision.

Other human studies include a health survey looking at effects of inhalation of airborne fluoride from coal combustion in China on urinary markers of kidney function. It is likely that the coal smoke contains many other chemicals, and it is not possible to dissect out the effects of fluoride. Another study looked at urinary markers of kidney function in children in China exposed to different levels of drinking water fluoride (<1 to >3.0mg/L). Children with enamel fluorosis and exposed to 2.58mg/L and children exposed to 4.51mg/L were reported to have impairments in the markers of kidney function. Although children were reported to have similar ages, gender, and nutritional status, other confounders may have been having an effect. In addition, overall fluoride exposure may have been higher than indicated by drinking water levels because of high fluoride coal exposure, or brick tea consumption. This study has limited applicability to Southampton, as the drinking water fluoride levels considered are higher than the proposed level of 1mg/L, and because the Chinese setting is
likely to differ greatly in factors such as lifestyle, socioeconomic status, and healthcare provision, in a way which could affect the results.

The chapter also looks at fluoride toxicity in kidney dialysis patients. Most of the studies did not report fluoride exposures of the patients; rather they just looked at their serum fluoride concentrations. The fact that serum fluoride levels are not necessarily indicative of clinical adverse effects, the lack of quantification of fluoride exposure, or comparison with lower fluoride exposure groups mean that this information is not helpful in determining risks at different concentrations of fluoride exposure. A few studies reported clinical outcomes such as bone and joint pain in these patients, but it was not possible to rule out non-fluoride causes for these outcomes as there was no comparison with groups with lower fluoride exposures or serum levels of fluoride. One study looked at effects of accidental use of water with “excessive” levels of fluoride in dialysis. However, this study is not likely to be representative either of what would happen to haemodialysis patients drinking water containing fluoride, or of the general population exposed to drinking water fluoride.

**Hepatic system**

This chapter reported some studies looking at liver damage or harm from fluoride. The authors describe mechanistic reasons why the liver might be affected by fluoride, but mechanistic rationales cannot prove an effect. They also cite six studies in animals, but these may not necessarily be representative of effects in humans. They also describe one clinical trial that looked at the effect of sodium fluoride supplementation (23g daily for 18 months) on people with osteoporosis. Although the study found increases in liver function enzymes compared to controls, the levels were still within normal ranges. This study does not apply to the Southampton setting because the levels of fluoride taken are higher than those that would be expected with drinking water at 1mg/L fluoride.

**Immune system**

The chapter cites three small case series of people reporting skin irritation after initiation of water fluoridation from the 1956 to 1977, and refer to blinded experiments suggesting that these were as a result of chemicals in the water supply. However, they say that the anecdotal reports of symptoms such as oral ulcers, urticaria, skin rashes, nasal congestion and epigastric distress do not fit any of the American Academy of Allergy categories of hypersensitivity. They suggest that the patients might be sensitive to the water fluoridation chemicals, silicofluorides, rather than fluoride itself. They say that a study found that human leukaemic cell lines were more susceptible to sodium hexafluorosilicate than sodium fluoride. However, studies in cell lines in vitro, where cells are directly exposed to chemicals, may not represent what would happen in the human body. Therefore more evidence from human studies would be needed to back up this claim.

They give mechanistic reasons why fluoride might affect the immune system, and report on animal studies and in vitro studies in human and animal cells. These are not sufficient evidence to prove an effect in vivo in humans.

The reports of skin irritation were to fluoridated water at 1mg/L, and therefore potentially relevant to Southampton. However, this small number of sporadic reports cannot indicate the proportion of the population which experienced these effects (as there is no denominator number of exposed people, and no systematic ascertainment of the numbers of people experiencing these effects) or prove that fluoride caused the effects seen.
Chapter 10: Genotoxicity and Carcinogenicity

Key messages
The authors report that the evidence regarding genotoxicity and carcinogenicity is mixed and tentative. Their overall conclusion drawn from the “weight of evidence” approach appears to differ from the conclusion they draw based solely on human studies. The “weight of evidence” approach conclusion is that “fluoride seems to have the potential to initiate or promote cancers, particularly of bone”. However, they report that the evidence from human epidemiological studies “does not clearly indicate that fluoride either is or is not carcinogenic in humans”. This latter conclusion seems warranted given the evidence presented.

The human studies findings effects tended to do so in the context of carrying out multiple comparisons, which can increase the risk of finding significant results by chance. In some cases, these associations came from studies looking at people with high industrial exposures to fluoride.

Genotoxicity and carcinogenicity were not toxicities that contributed to the committee’s decision to recommend lowering the MCLG. If fluoride was a known or probable human carcinogen the MCLG would have to be set at zero, but such a recommendation was not made by the committee.

Summary of ‘Findings’
The chapter’s conclusions include:

- Fluoride seems to have the potential to initiate or promote cancers, particularly of bone, but the evidence is tentative and mixed. Osteosarcoma was a particularly noted as a concern based on knowledge of fluoride biology (deposition in bone, and ability to induce bone cells to divide), as well as results of animal studies and some human epidemiological studies with mixed results.

- A number of studies have been published since the previous NRC review in 1993, including studies finding at least some positive associations with one or more types of cancer, and some in vivo studies suggesting fluoride is capable of damaging chromosomes. Human epidemiology studies are described as mixed and equivocal.

- Studies in male rats have shown a positive trend in the relationship between fluoride and osteosarcoma, although not all studies were positive. However, it was noted that rats have different development of the long bone to humans, and that human osteosarcomas commonly occur in these bones. The authors note that most of the rat osteosarcomas did not occur in the long bones. They report one study in rats investigating radiation as a

- The authors note that the previous NRC review in 1993 concluded that osteomas in mice were related to fluoride exposure, and they believe that this still remains important to the overall weight-of-evidence consideration. They also cite one study in female rats showing an increase in incidence and severity of osteosclerosis with high dose fluoride.

- Data on genotoxicity from humans is conflicting, particularly data from in vivo human studies. Five studies were reported to be positive based on ingestion or inhalation of fluoride, but the studies were reported to have flaws, including lack of information about participant selection and comparability of exposed and unexposed participants, or inability to rule out confounding. Studies with negative findings were also noted.
Bazian’s critique of this chapter (validity and applicability)

In vitro studies looking at the possibility of genotoxicity of fluoride in human and other cells are reported, as well as studies of genotoxicity and carcinogenicity effects in in vivo studies in animals (mice and rats). These studies mostly used sodium fluoride. Extrapolating from animals and in vitro studies to humans is complicated by inter-species differences and differences in how cells grown in the laboratory and the human body as a whole are exposed and react to chemicals. Although the authors report taking several important considerations into account when determining the applicability of such studies to humans, the findings of these studies should still only be tentatively extrapolated to humans, and findings need confirmation in human studies.

Genotoxicity

The in vivo human genotoxicity studies reported looked at ingestion, inhalation and skin contact routes. The authors note that these observational epidemiological studies have the advantages of looking at relevant concentrations of fluoride in in vivo physiological conditions. However, they do also note that they have the inherent limitations of studies of this type, in that it is not possible to be certain that all potential confounders have been controlled for.

The inhalation/skin contact studies are not likely to be relevant to Southampton, where fluoride will be in drinking water. The ingestion studies were mostly carried out in India and China and involved drinking water. The high drinking water fluoride regions they considered had higher concentrations of fluoride than 1mg/L (1.95 to 15 mg/L), One study included areas with 4.4mg/L, 1mg/L, and 0.2mg/L fluoride, but no results comparing the 1mg/L group with the lower fluoride area were reported in the review. These studies mostly looked at presence of cytogenetic changes (mainly sister chromatid exchange - a swapping of genetic material between the two identical copies of a chromosome) in lymphocytes. Although this test is reported to be predictive of carcinogenicity, it is still a proxy outcome, and a clinical outcome such as rate of cancer is preferable. One study compared bone fluoride in 20 people with osteosarcoma in India, with that of the general population. However, the small size of this study, the possibility of selection bias and confounding, the lack of information on fluoride exposures, and the fact that some of the concentrations of fluoride were reported to exceed the theoretical maximum level in bone mean that this study lacks reliability.

The results reported from these studies are for levels of drinking water fluoride higher than 1mg/L and therefore the results are not directly applicable to Southampton. In addition, in China at least, exposure to non-drinking water sources such as high fluoride coal or brick tea could increase fluoride exposure above that which is expected from looking at drinking water alone. The other differences between these countries and the UK, for example in terms of standard of living and healthcare provision also limit their applicability.

Carcinogenicity

The authors note that detecting relatively small effects of fluoride or other environmental chemicals on cancer incidence is difficult for a number of reasons, including the long time period between exposure and development of cancer, migration of individuals between exposed and unexposed areas affecting classification when exposure is assessed at the population level, and the need to examine each type of cancer separately.

The chapter authors report basic criteria for evaluation of the quality of such studies. It was not clear whether they had applied these in a systematic way to the studies they evaluated. They say that
using biological plausibility criteria and a weight-of-evidence approach is necessary to determine whether associations seen are causal.

The new carcinogenicity literature identified in this review included five ecological studies as well as three case-control studies and a historical cohort study. The book authors point out a number of weaknesses of the ecological studies, including statistical or data analysis flaws, combining all cancers, and use of multiple comparisons (which can increase the likelihood of getting a significant result just by chance). Because in ecological studies no individual level information is available, individual level confounders cannot be adjusted for, and this type of study is particularly susceptible to confounding.

Another potential limitation of these studies is that if they solely looked at fluoride exposure in drinking water (which seems likely given that no individual level data was collected) and other sources of fluoride were contributing to overall exposure the level of drinking water fluoride may not correlate well with overall fluoride exposure. If the two groups being compared have similar non-drinking water fluoride exposures this would not create a problem, but if the groups have differing non-drinking water exposures then results may be misleading. This could particularly be a concern for worldwide comparisons, where groups have greater chance of having varied non-drinking water fluoride exposures.

The results of the ecological carcinogenicity studies were not presented so that a particular drinking water concentration (such as 1mg/L) could be compared with a lower concentration. The methodological weaknesses of these studies mean that they lack validity and require confirmation.

**Bone and joint cancers, particularly osteosarcoma**

One of the main cancers of interest was osteosarcoma, this is because of the effect fluoride has on bone cells. The evidence reviewed in 1993 about osteosarcoma was all ecological or partially ecological, and results were reported to be contradictory and inconclusive. The new studies identified in the current review included three case-control studies that looked at the rate of bone cancer or osteosarcoma, and a cohort study. The cohort study looked at the effects of exposure to a high fluoride compound called cryolite on production workers. This study is not applicable to Southampton, as the workers had a much higher exposure to fluoride (30mg/day) than would be expected from drinking fluoridated water at 1mg/L.

The case control studies do carry the advantage of individual level analysis of exposure and outcome, and the ability to control for confounding, they are still susceptible to bias and residual confounding. For example, exposures are reported retrospectively which may reduce accuracy, there may also be systematic differences in how people with a disease (cases) recall their exposures compared with those without, particularly if they attribute their cancer to a particular exposure. In addition, selection bias may also be a problem if those selected to take part are not representative of all individuals with the disease, or if controls are not selected appropriately to match the cases.

**Bladder cancer**

One of the ecological studies from Taiwan looked at areas of natural fluoridation (mean about 0.25mg/L, range not reported), and only found a significant difference in the rate of bladder cancer in women. As this study carried out multiple comparisons, it is more likely that it would find differences by chance. Therefore its results should be interpreted cautiously. As the specific concentrations of fluoride compared were unclear, it is also difficult to extrapolate to other settings.
Oro-pharyngeal cancer

An older study from England found an increase in oro-pharyngeal cancer in women was found with exposures to water with over 1mg/L fluoride naturally, but again there were many comparisons, which reduces reliability of results. The concentrations in this study exceed those proposed in the South Central Area and results are not directly applicable.

Uterine cancer

One study from Japan used an ecological before and after design. It looked at rates of mortality from uterine cancer before and after the termination of water fluoridation. All fluoride concentrations were reported to be below 0.4mg/L. The rates of mortality were reported to converge with those in non fluoridated towns after termination of fluoridation. However, over time, changes in confounders over time cannot be ruled out as a potential explanation for these results. The Taiwanese ecological study did not find a significant association between uterine cancer mortality rates and fluoride exposure.

Two of the case-control studies concluded that there was no association between osteosarcoma and fluoride, but it was unclear exactly what levels of exposure were experienced in case and control groups and therefore the relevance to the South West SHA setting. The third case-control study from the US (91 cases and 188 controls) was part of an unpublished dissertation, which is publicly available. This study found some evidence of an association between exposure to target water fluoridation levels (about 1mg/L) in boys ages 6 to 8 years old and osteosarcoma in an exploratory analysis. Although not explicit, this comparison may have been of artificially fluoridated water. However, the book’s authors expressed concern that the controls used, who came from the same orthopaedic departments, may not be representative enough of the population. In particular, if fluoride was to affect fracture risk in either a positive or negative way, then orthopaedic patients with fractures would be expected to differ in their fluoride exposure from the rest of the population, and this could bias the results of the comparison with cases. In addition, assessment of possible confounders such as individual socioeconomic status and education was not carried out and little data was reported to be presented in the results section. As an unpublished piece of research it will not have undergone the peer review process, which ensures that research is robust enough for publication. Although this study appears potentially relevant to Southampton, the limitation described mean that the results of this analysis should be considered preliminary pending publication.

The chapter concludes that the epidemiological literature described did not clearly indicate that fluoride was or was not carcinogenic in humans. This conclusion seemed valid based on the evidence presented.
Chapter 11: Drinking water standards for Fluoride

Key message
The NRC committee on drinking water fluoride recommended lowering of the EPA’s MCLG for fluoride in drinking water of 4mg/L. They make this recommendation following a consensus judgement that the current MCLG did not protect the public adequately from severe enamel fluorosis, stage II skeletal fluorosis, and bone fractures.

This conclusion is not of direct relevance for the population of Southampton, as the European Union maximum permissible level (1.5mg/L) is already lower than the MCLG, and the level of fluoridation proposed for Southampton is less than this.

Based on the evidence presented in this book, severe enamel fluorosis and stage II or III skeletal fluorosis are likely to be extremely rare with drinking water fluoride at 1mg/L, and this level does not significantly increase fracture risk.

Summary of ‘Conclusions’
The review concluded that:

- The EPA’s MCLG of 4mg/L should be lowered to prevent children developing severe enamel fluorosis and reduce the lifetime build-up of fluoride in the bones that the majority of the committee judged to be likely to increase risk of fracture and possibly skeletal fluorosis. These are particularly of concern in subpopulations prone to accumulate fluoride in their bone.

- At concentrations under the current SMCL of 2mg/L fluoride, the prevalence of severe enamel fluorosis is very low. However, this level does not completely prevent moderate enamel fluorosis. The SMCL was intended to reduce prevalence of enamel fluorosis to 15% or lower. The available evidence suggests that fewer than 15% of children would experience moderate enamel fluorosis of aesthetic concern (i.e. discolouration affecting the front teeth) at this level. It is not known whether moderate enamel fluorosis might cause adverse psychological effects or adversely affect social functioning. Further research is needed consider this and other issues.

Bazian’s critique of this chapter (validity and applicability)
In drawing their overall conclusions, the authors report that they considered whether the MCLG was adequately protective against severe enamel fluorosis, clinical stage II skeletal fluorosis, and bone fractures. The book authors report that these three toxicities were assessed because there was enough relevant data on which to base a judgement. From the evidence presented in the book, these appeared to be the areas which had the greatest amount of human research.

For severe enamel fluorosis, the authors discuss the rationale behind their suggested re-classification of the condition as an adverse health event. This decision appeared to be based on the general consensus in the dental literature about the adverse dental effects of severe enamel fluorosis, and the fact that the condition is treated by dentists to prevent further damage to the enamel and for cosmetic reasons. There was no new evidence presented specifically regarding this issue. The majority of the committee agreed with this decision (10 out of 12 members) the other two did not. There was unanimous agreement that the MCLG should prevent against this condition.
The recommended re-classification of severe enamel fluorosis as an adverse health event appears to be a decision based largely on expert opinion rather than direct evidence of adverse outcomes. The authors acknowledge that whether it increases the risk of dental caries has yet to be firmly established.

The evidence that severe enamel fluorosis has a near zero prevalence at water levels of less than 2mg/L is based on a large number of studies in young people aged under 20 years old in the US, that show a clear trend in prevalence. As such this information appears relatively robust. It remains to be seen whether reducing fluoride levels in water from 4mg/L to 2mg/L can reduce prevalence of severe fluorosis.

The conclusions about skeletal fluorosis are also based on a re-classification. The original MCLG was set to minimise crippling (clinical stage III) skeletal fluorosis, as this was judged to be an adverse health effect, while less severe forms of skeletal fluorosis were not. However, the committee thought that clinical stage II, the symptoms of which include chronic joint pain and arthritic symptoms, should now be classified as an adverse health effect. This reclassification appeared to largely be based on expert opinion rather than any new evidence. The conclusion that stage II fluorosis can occur with lifetime exposure to 4mg/L drinking water fluoride is largely based on extrapolation rather than direct evidence. There is little evidence about the prevalence of stage II skeletal fluorosis in the US, and stage III skeletal fluorosis is rare. The evidence suggesting that stage II fluorosis could occur with drinking water at 4mg/L drinking water comes from comparisons of estimated levels of fluoride that could build up in bone with lifetime exposure to 4mg/L drinking water with levels of fluoride in bone that comes from people with skeletal fluorosis. This method of estimation should be considered very tentative. The estimations of lifetime fluoride build-up are based on pharmacokinetic modelling, and their reliability will depend on the accuracy of the underlying assumption. The historical estimations of the level of fluoride in bones from people with stage II or III skeletal fluorosis are based on small numbers of people, and appear not to have been compared with levels in people without skeletal fluorosis.

In addition, the book described various revisions to the way that risk assessment is carried out by the EPA, and how they set drinking water standards that have been made since the MCLG and SMCL for fluoride were set. The existence of these new procedures is likely to also have contributed to the suggestion that the EPA carries out new risk assessments of fluoride.

Overall these conclusions should not be a cause for concern for people in Southampton. Although the committee suggest lowering the US EPA’s MCLG from 4mg/L, the UK already has a lower maximum permitted level for fluoride than the US (1.5mg/L). The proposed level of artificial fluoridation (1mg/L) in the Southampton region is lower than both the US MCLG and SMCL (4 mg/L and 2mg/L respectively).

The decision of the committee was based on three toxicities: severe enamel fluorosis, skeletal fluorosis, and bone fractures. The claim that the MCLG was not adequately protective against these adverse effects does not have direct relevance when deciding about fluoridation of water to a level of 1mg/L fluoride.

In the case of severe enamel fluorosis, a large number of studies found that the prevalence of this condition among people aged 20 years or younger in areas with drinking water of <2mg/L fluoride was nearly zero in the US. Based on these studies, use of artificial fluoridation at 1mg/L is likely to be associated with a near zero risk of severe enamel fluorosis.
In the case of bone fractures, the book did not assess the risks of fractures with fluoride at 1mg/L. However, it did identify a systematic review by the University of York which assessed these risks. The systematic review found no significant increase in the risk of fractures. None of the additional studies identified in the book were likely to affect this finding, as they found either no significant difference or a benefit with fluoridation at 1mg/L compared to lower levels. The findings of this systematic review are more directly applicable to the South Central SHA setting than the assessment performed in this book.

In the case of skeletal fluorosis, as described above, the reclassification of stage II skeletal fluorosis as an adverse health effect implies the need for a lowering of the MCLG, as the current MCLG was set to avoid the more severe stage III skeletal fluorosis. However, even at the current MCLG, stage III skeletal fluorosis is reported to be rare, and there have been no clearly described cases of stage II fluorosis. This suggests that such cases are likely to be even rarer in the UK in areas with artificial fluoridation at levels of 1mg/L.
4. References


5. Abbreviations and Acronyms

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<tbody>
<tr>
<td>AIF</td>
<td>Aluminium fluoride</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Protection</td>
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<td>EPA</td>
<td>Environmental Protection Agency</td>
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<td>F</td>
<td>Fluoride</td>
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<td>MCL</td>
<td>Maximum Contaminant Level</td>
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<td>MCLG</td>
<td>Maximum Contaminant Level Goal</td>
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<tr>
<td>mg/L</td>
<td>Milligrammes per Litre</td>
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<td>NaF</td>
<td>Sodium fluoride</td>
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<td>NRC</td>
<td>National Research Council</td>
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<td>ppm</td>
<td>Parts per million</td>
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<td>SHA</td>
<td>Strategic Health Authority</td>
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<td>SMCL</td>
<td>Secondary Maximum Contaminant Level</td>
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