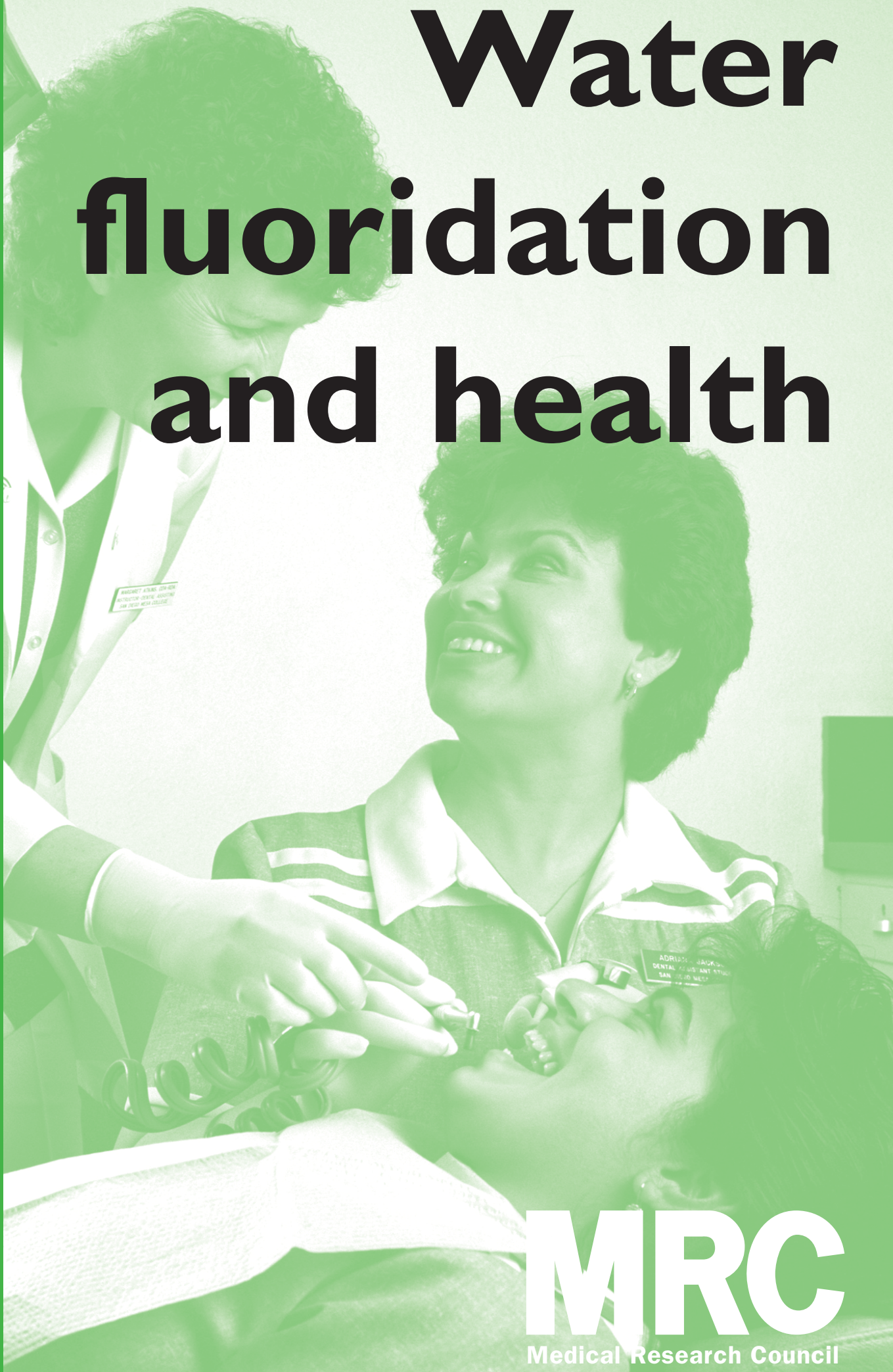


Working group report

Water fluoridation and health



MRC
Medical Research Council

Lay summary

The practice of adding fluoride to drinking water to improve dental health has been endorsed by numerous national and international health institutions, including the World Health Organization. It has been argued that in communities with piped water supplies it is the most cost effective method of reaching the whole population, particularly children with a high risk of tooth decay.

Much of the evidence that links water fluoridation to improved dental health comes from research conducted several decades ago. The Department of Health therefore commissioned the NHS Centre for Reviews and Dissemination at the University of York to produce an up to date review of the topic, looking at all relevant studies.

The York review, published in September 2000, confirmed the beneficial effect of water fluoridation on dental caries (cavities), but also highlighted the increased prevalence of dental fluorosis (a defect of the enamel ranging from mild speckling to more gross effects) associated with fluoridation. The review concluded that little high quality research had been carried out on the broader question of fluoride and health, and that the available evidence did not allow confident estimates to be made of other possible risks to health or of the benefits of water fluoridation in reducing dental health inequalities.

In light of these findings the Medical Research Council, at the request of the Department of Health, set up the present Working Group to consider what further research is required to improve knowledge about fluoridation and health. This report aims to identify areas of uncertainty regarding the balance of benefits and risks of water fluoridation, and to make appropriate recommendations for research to address these uncertainties.

With regard to public knowledge and understanding of the fluoridation issue, this report identifies additional information needed by the public to make informed decisions. For example, better information is needed on the prevalence of different forms of dental fluorosis (and their visual/aesthetic impact) and on similar looking tooth defects that are not associated with fluoridation.

Because of the wide use of toothpastes and other dental health care products containing fluoride, and the potential for fluoride exposure from a number of other sources, it is especially important to understand better the total exposure that individuals are experiencing. This knowledge should then be used in any future studies on the impact of water fluoridation. It is also important to gain a better understanding of any differences there might be in the uptake of fluoride from artificially fluoridated as opposed to naturally fluoridated water, and to determine the impact, if any, of the level of water hardness. Trends in fluoride exposure, especially in children, need to be tracked.

Research recommendations on caries include the need to study the impact of water fluoridation on caries reduction in children against a background of widespread use of fluoride toothpaste, and to extend knowledge on how the effects of water fluoridation vary with social class. There is also a need to understand better the economic impacts and the effects of fluoridation on health and well-being beyond the usual measures of decayed, missing or filled teeth. Further work is warranted on the effects of fluoridation on dental health in adults.

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The public's level of awareness and understanding of dental fluorosis is generally low. Future research should aim to improve this situation as well as improving knowledge on the incidence and severity of fluorosis. Research is specifically recommended that determines the prevalence of dental fluorosis in fluoridated and non-fluoridated communities and establishes the public's perception of fluorosis.

There is almost universal agreement that tooth decay in children is related to social class. The majority of the research conducted to date indicates that water fluoridation reduces dental caries inequalities between high and low social groups. No studies have shown fluoridation to increase inequalities. Further studies are recommended that look at appropriate measures of social inequalities related to water fluoridation, dental caries and fluorosis, taking into account important factors such as use of fluoridated toothpaste and dietary sugar ingestion.

There are a number of possible health outcomes (other than dental health) related to water fluoridation. The possibility of an effect on the risk of hip fracture is the most important in public health terms. The available evidence on this suggests no effect, but cannot rule out the possibility of a small percentage change (either an increase or a decrease) in hip fractures. Current estimates of the size of any effect are based on a combination of studies of naturally and artificially fluoridated water. If studies show that the uptake of fluoride from artificially fluoridated water is substantially higher than from naturally fluoridated water (see above), then it will be necessary to investigate further the relationship of hip fractures specifically to long term consumption of artificially fluoridated water. Research results currently available do not allow a useful estimate to be made of the impact of fluoridation on other bone disorders. However, the few studies that have been carried out do not suggest a problem and studies on such diseases are considered of lower priority.

Another issue is the possible role of fluoride and fluoridation on cancer incidence. Although available evidence suggests no link between water fluoridation and either cancer in general or any specific cancer type (including osteosarcoma, primary bone cancer), an updated analysis of UK data on fluoridation and cancer rates is recommended. Also, if new studies are undertaken on the incidence and causes of osteosarcoma then fluoride exposure should be assessed together with the other possible risk factors.

Additional health outcomes suggested by some to be associated with fluoride ingestion include effects on the immune system, reproductive and developmental (birth) defects, and effects on the kidney and gastrointestinal tract. Other concerns are related to the chemicals that are added during the fluoridation process, and to indirect effects such as increased leaching of lead from pipes and aluminium from cooking utensils and altered uptake or toxicity of these substances. There is no evidence for any significant health effects of this type and no specific research is recommended, although it is appropriate to keep the area under review.

I. Introduction

I.1 Background to the review

In September 2000, the NHS Centre for Reviews and Dissemination at the University of York published a systematic review of epidemiological studies on water fluoridation and health (NHS CRD, 2000). The review had been commissioned by the Chief Medical Officer of the Department of Health (DH) in recognition of the fact that much of the research evidence linking water fluoridation to improved dental health had been undertaken several decades earlier (see 'Our Healthier Nation', paragraph 9.20).

The York Review confirmed the beneficial effect of water fluoridation on dental caries, but also suggested that this should be considered alongside the increased prevalence of dental fluorosis. Another key conclusion of the review was that little high quality research had been undertaken in the area of fluoride and health more broadly. The available research evidence was considered insufficient to allow a confident estimate of the risks that might be associated with non-dental health outcomes or of the potential benefit of water fluoridation on health inequalities associated with dental caries.

In light of these findings, DH approached the Medical Research Council (MRC) to take forward the conclusions and recommendations of the York Review and consider what further research might be required to improve the evidence base in the area of fluoride and health. The MRC established a Working Group to identify where the existing knowledge base and public health policy might benefit from further research, and how this evidence might best be obtained.

The terms of reference of the Working Group were to:

- Provide advice on current scientific evidence regarding the health effects of fluorides in the context of water fluoridation;
- Consider what further research in this area might be required and what priorities should apply to usefully inform public health policy in this area;
- Report to the MRC Physiological Medicine and Infections Board and the MRC Health Services and Public Health Research Board; and
- Report to the Department of Health.

The Working Group¹ met five times between February and November 2001. The conclusions and research recommendations of the Working Group are encapsulated in this report (which is to be considered by the relevant MRC Research Board(s) prior to submission to the Department of Health.)

I.2 Structure of the report

The report contains five main sections in addition to this scene-setting introduction. Section 2 takes a broad look at risk assessment issues, including the public perception of risk. Section 3 covers the important issue of total exposure; fluoridated drinking water is just one of many potential sources of fluoride to which people are exposed. The principal health outcomes associated with fluoride exposure are addressed in section 4, which includes consideration of the effects of social class. Section 5 discusses other potential health outcomes, including those for which there is little available evidence, and also considers some indirect effects of adding fluoride to drinking water. All these sections of the report

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contain research recommendations; the purpose of section 6 is to present the key conclusions of the report and to list those recommendations that are considered most important.

1.3 Fluoride and fluoridation

Fluoride occurs naturally in soil, water, plants and animals in trace quantities. In groundwater, natural fluoride concentrations range from trace quantities to over 25mg/l.

When fluoride is ingested by humans and other animals, some is taken up by body tissues, with long-term deposition in teeth and bones. The fluoride content of tooth tissues reflects the biologically available fluoride at the time of tooth formation – after which time, except for the outermost layer of the enamel, fluoride levels remain constant (WHO, 1994).

Early epidemiological studies, comparing local populations using both observational and quasi-experimental designs, had indicated a significant reduction in dental caries in childhood within populations exposed to higher levels of fluoride in drinking water. Accordingly, in 1952, on the recommendation of the MRC, the British Government initiated a study into water fluoridation with a view to advising whether fluoride should be added to drinking water supplies in the UK (HMSO, 1962; HMSO, 1969). As a result, a number of Local Authority water fluoridation schemes were introduced in England and Wales between 1964 and 1975. Some five million people now receive water in which the fluoride content has been artificially increased to a level of one part per million². Major schemes are in operation in Birmingham and throughout the West Midlands, and also in Tyneside. In addition, about 500,000 people in this country receive water which naturally contains fluoride at or about the level of one part per million. A further one million people receive water which naturally contains fluoride at a lower level, but which is still considered to confer some dental benefits (House of Commons Official Report, 1998).

The Water (Fluoridation) Act 1985 required District Health Authorities to consult widely in determining their policy on water fluoridation, but water fluoridation continues to be an emotive issue. Opponents tend to view it as an infringement of personal rights, and/or believe that it causes ill health. In contrast, proponents consider it a safe, simple, and cost-effective public health measure to reduce the incidence of dental caries (Hamilton, 1992). The practice of fluoridating water has been endorsed by (inter alia) the World Health Organization, the British Medical Association, the Faculty of Public Health Medicine, the British Dental Association and, in the USA, by the Surgeon General, the American Medical Association and the American Dental Association.

It has been argued that, if the community has a piped water supply, water fluoridation is the most cost-effective method of reaching the whole population, including children at highest risk (Akenhurst & Sanderson, 1994). However, there are potential health disbenefits of fluoride that have to be considered (see Table 1), and also various additional potential sources of exposure. This report aims to identify any areas of uncertainty about the balance between the benefits and disbenefits of water fluoridation, and to make appropriate recommendations for research to remove or reduce these uncertainties.

2 According to Hamilton (1992) the concentration of fluoride in water required for prevention of dental caries is generally agreed to be in the range 0.7-1.2mg/l, although the 1994 WHO report stated that “the world optimum concentration would normally be in the range 0.5 – 1.0 mg/l”. In the UK, concentrations of 0.3-0.7mg/l are considered to afford below optimal protection against tooth decay, and at less than 0.3mg/l it is said to be doubtful whether any benefit is gained (Murray et al., 1991).

Table 1: Exposure to fluoride and associated adverse effects

Exposure to fluoride (mg/l drinking water)	Age	Effect
≥2	Child	Dental fluorosis
≥8	All ages	Skeletal fluorosis
≥50 (12hours)	All ages	Gastroenteritis
Pathological doses for exposures other than drinking water		
5-20 mg/m ³ air (occupational)	Adults	Crippling fluorosis
2,500-10,000 mg oral	Adults	Acute lethal dose
≥16 mg/kg oral body weight	Child	Acute lethal dose

Adapted from NHMRC, 1991

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2. Risk assessment, management and perception

Making decisions on whether to add fluoride to drinking water (or cease fluoridation) entails a two stage process of risk assessment and risk management. Implementation of the latter should be informed by an awareness of the public's perception of the risk.

2.1 Risk (and benefit) assessment

Risk assessment involves first identifying the potential adverse outcomes (hazards) from a policy, action or situation, and then estimating the chance and likely extent (risks) of their occurrence in those who might be affected, including any particularly vulnerable subgroups.

Depending on the extent and quality of the scientific evidence underpinning this process, estimates of risk may be subject to significant uncertainty. In such situations the extent of the uncertainty should be estimated – ie the range within which risks might reasonably be expected to lie, given what is known.

In the same way that the risks (adverse consequences) arising from a policy or action are estimated, it is also necessary to assess the likely magnitude of any benefits that might accrue. Again, where there are important uncertainties, these must be recognised and as far as possible quantified.

2.2 Risk management

Once the risks and benefits have been assessed, this information must be set alongside other considerations, such as the financial cost of the policy or action, and a decision then made on whether to implement the change. This is not simply a matter of science - it involves value judgements, and individuals may weigh the risks, benefits and attendant uncertainties differently. If the decision must be taken at a community level (as with water fluoridation), it often falls to democratically elected representatives and may follow wider public consultation and debate.

In the case of water fluoridation, information about the nature and likely extent of the benefits and the possible adverse effects comes mainly from pharmacology, toxicology and epidemiology. Pharmacology and toxicology provide evidence on the types of benefit and hazard that could plausibly occur, how these effects might relate to exposure to fluoridated water over time (eg would they be relatively immediate or delayed), subgroups who might be unusually susceptible and, to some extent, the potential frequency of the outcomes. Epidemiology provides more direct evidence on the occurrence of beneficial and adverse effects in affected populations.

There is a range of known or possible impacts of fluoride supplementation on health, some beneficial, some detrimental (see Sections 4 and 5). Some of these effects accrue early (eg reduction in childhood dental caries) while others may occur later (eg any contributions to skeletal fluorosis and other aspects of bone health).

From a public health perspective, the aim is to optimise the overall improvement in population health, while taking account of any differences in susceptibility within the population. To achieve this requires quantitative estimates of the various dose effect relationships, and the capacity to titrate qualitatively different health outcomes against one another (eg reduction in dental caries versus increase in dental fluorosis). In the absence of an agreed, universally applicable, common metric (of which the disability adjusted life year, or DALY, is the current prime candidate within WHO), such comparisons cannot be performed objectively and precisely. Hence, the inevitability of using, at least in part, expert and political judgement to evaluate the pros and cons of fluoride supplementation.

2.3 Public perception of risk

2.3.1 Achieving informed public debate about complex risk/benefit information

There is a growing appreciation of the need for more public information and education in the area of health risk and for a constructive dialogue between scientists, policy makers and the public on such issues. Both DH and the Department for Environment, Food and Rural Affairs (DEFRA) are currently looking at these issues. The presentation of this type of information to the public needs to be jargon free and should not assume high levels of statistical or other technical awareness. The communication of complex choices where the benefits and risks are of very different types, as is the case with water fluoridation, must be done in a way that increases the probability that those choices will be well informed. On any given topic, there may be tensions arising from opposite viewpoints.

2.3.2 Presenting to the public the inevitability of uncertainty in research findings

In an era when 'science' is under increasing public and political scrutiny, and in which the media can generate unrealistic and unachievable expectations of certainty or 'proof', there is a need to communicate honestly and openly about the levels of certainty that can and cannot be inferred from research findings. Uncertainty is an inherent feature of science and medicine, but this is a concept that seems not to be well understood by the public.

2.3.3 Explaining the concept of different strengths of evidence to the public

It is important to explain simply the concept of differing 'strengths' of evidence that can be derived from different types of research design, as well as the changing methodological standards that have been used in research over time. For example, it is unrealistic in many fields to expect a study carried out in the 1970s necessarily to conform to the methodological standards judged appropriate in the 2000s. Also, the quality of research published on the Web and in other non-peer reviewed sources is unlikely to match that of research published in the standard scientific journals, and therefore generally carries little weight. Some members of the public (and many health professionals) may not yet be used to these concepts.

2.3.4 Public perception of fluoridation

There has been limited dialogue with the general public on the fluoridation issue. A study with focus groups in three non-fluoridated areas of England (Hounslow, Leeds and Oldham) indicated that members of the public wish to be informed of water fluoridation plans but do not see themselves as being appropriate arbiters of decisions about implementation (Lowry et al., 2000). However, even where the public does not wish to make decisions, this does not imply that this opportunity should be withdrawn.

2.3.5 Information needs

Listed below are some specific issues that could usefully be communicated to the public about water fluoridation:

- The actual coverage of water fluoridation in the UK at present (many assume it is more widespread than it is)
- The consequences of not preventing dental caries – costs, morbidity and mortality
- The strength of evidence on the efficacy of (and problems associated with) alternatives to water fluoridation
- The nature, effects and degree of aesthetic impact of dental fluorosis

2.3.6 What is most important to the public?

The common sense view is that benefits should outweigh the risks. Both preventive benefits and potential harms must be set out clearly and consistently to avoid confusion and mixed messages to the public. Of course, the public may view the potential harm as more significant than the benefits, even

though the numbers involved might be much smaller; people may feel that they are being asked to compare apples and oranges.

In the USA a decade ago the concept was advanced that the public's perception of health risk was influenced more by potential 'outrage' than by the magnitude of the potential risk. A series of strategies was advocated for reducing outrage (through information provision), as it was felt that the public could not make informed decisions in the presence of outrage (Sandham, 1990). A Canadian telephone survey of 2000 people living in fluoridated and non-fluoridated municipalities in 1998 indicated that in both areas knowledge about caries preventive benefits was low and knowledge about dental fluorosis was very low. The authors concluded that there was still a need for public health education on the uses of fluoride (Levallois et al., 1998). There are a number of market research reports on public opinion (including one in Anglesey after water fluoridation was withdrawn) that might be informative (Hulse et al., 1995).

2.3.7 Implications for prioritising research on fluoridation

There are several areas where further information could help the public make informed decisions:

Clarity is required about the prevalence of different forms of dental fluorosis. It is important to separate out discussion on the mild and moderate forms from the rare severe form.

The role of impacts on tooth mineralisation **not** associated with water fluoridation also needs clarifying. Many aesthetic defects are caused by other insults and fluoride related opacities may be associated with over-use of topical products rather than sustained low dose acquisition through water.

More robust information on the potential harms of fluoridation is needed.

In addition, knowledge is needed on the public perception of the aesthetic impairment associated with different types of dental fluorosis. There is some evidence from large population samples (Scottish Health Board's Epidemiological Programme 1991–2000: Pitts et al., 1993, 1995, 1997, 1999) that children are unaware of much of what dentists may score as mild or moderate fluorosis. For example, of 5,981 14-year-old children examined in non-fluoridated Scotland, 750 had a degree of fluorosis like defects recorded by dental examiners. However only 45 (0.75% overall) of these were judged by dentists to be of noticeable aesthetic impact and were noticed by the children themselves. Other work is being carried out using lay 'juries' to assess photographs of different severities of fluorosis.

As a more general point, scientists undertaking research in this area (and those commissioning it) should build in provision for public engagement. They need to be sensitive to the needs of the public and the results of such work must be communicated in a way that can be readily understood.

2.4 Research recommendations

Further work in this field should cover four main areas:

- Research to evaluate methods for gauging public opinion, specifically on issues relating to water fluoridation.
- Increased understanding on how to engage the public more effectively when planning research.
- Research to assess methods for communicating scientific results to the public.
- Improved involvement of public opinion in reaching policy decisions.

Some such work is already in progress or has taken place (eg Hughes & Lawther, 1993).

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3. Total fluoride exposure and uptake

In order to assess the specific benefits and/or hazards that might arise from the fluoridation of water, it is necessary to take account of the different sources and routes of human exposure to fluoride and to understand the absorption, distribution and metabolism of fluoride in the human body. This information is relevant for several reasons:

- Estimates of the impact of water fluoridation on total exposure to fluoride may otherwise be inaccurate or misleading.
- The effects of water fluoridation might be confounded or modified by exposure to fluoride from other sources.
- If other sources of fluoride are important determinants of total dose in some individuals, they might be a useful focus for epidemiological studies that could help to inform risk assessment.
- If the bioavailability of ingested fluoride can vary significantly, this might need to be taken into account in the interpretation of epidemiological studies.
- Knowledge of the distribution and metabolism of fluoride may provide pointers to the measures of exposure (eg recent or cumulative) that are most relevant to different health outcomes, and to the plausibility of effects in different tissues.
- It may enable the establishment of useful biomarkers of internal dose for use in epidemiological studies of health effects.

3.1 Uptake, distribution, metabolism and excretion of fluoride

The main route of fluoride absorption is through the gastrointestinal tract, although inhalation may be a relevant route of exposure in certain industrial situations.

Following ingestion, the fluoride ion is readily absorbed – primarily from the stomach and also the small intestine. Peak plasma levels normally occur during the first hour after ingestion. If the amount of fluoride ingested is small (no more than a few milligrams) soft tissue fluoride levels normally decline to those before ingestion within 3 to 6 hours. The degree of absorption of fluoride from ingested sources is influenced by a number of factors, some of which are poorly understood (Whitford, 1996). When a readily soluble compound such as sodium fluoride is ingested with water, nearly all the fluoride may be absorbed. If the fluoride is taken with milk or food, however, then the degree of absorption is reduced because of the formation of insoluble complexes or precipitates. High calcium content of co-ingesta (food and drink ingested at the same time) can further reduce the absorbed dose, and the pH of the stomach can influence fluoride absorption. The more acid the stomach, the more fluoride will be absorbed (Whitford, 1996).

The question of the bioavailability of ingested fluoride is important, especially with respect to the possible influence of water hardness on uptake and differences between naturally fluoridated and artificially fluoridated water. Inorganic ions in the water certainly can interfere with fluoride absorption, but at the 1 ppm fluoride level this interference is biologically insignificant in normally composed drinking water. Only at high concentrations of calcium, magnesium and aluminium ions is fluoride absorption effectively reduced, owing to formation of less soluble complex fluorides (Cremer & Buttner, 1970). Considering possible differences in bioavailability between naturally fluoridated and artificially fluoridated water, Cremer and Buttner (1970) concluded that “fluorides that either occur naturally in water or are added to communal supplies...to increase the fluoride level to 1ppm F, yield fluoride ions which are almost completely absorbed from the gastrointestinal tract”; however, this is an area of some uncertainty and debate, and requires further study.

The fluoride ion is primarily distributed in the body via plasma. The quantitatively most important fates of absorbed fluoride are uptake by calcified tissues and excretion in the urine (with a small amount excreted via sweat and faeces). On average, about half the absorbed amount is excreted in the urine, though this proportion varies considerably, and approximately 97-99% of the retained fluoride in the body becomes associated with bone and other calcified tissues (Hillier et al., 1996). However, the fluoride

of calcified tissues is not irreversibly bound, and if fluoride intake is reduced over a long enough time course the concentrations in bone, etc. will eventually reflect this change through the mobilisation of bound fluoride. Within the soft tissues of the body, fluoride rapidly establishes a steady state distribution between extracellular and intracellular fluids (Whitford, 1996).

3.2 Sources of fluoride exposure

The major potential sources of ingested fluoride are water and other dietary sources (including food and drinks prepared with fluoridated water), fluoride tablets and drops and other supplements (more relevant in the USA and elsewhere than in the UK), and unintentional ingestion of fluoridated toothpaste, especially by children, or fluoride mouth rinses. In addition, some individuals are exposed to fluoride occupationally, or receive therapeutic doses of fluoride (for example in the treatment of otosclerosis and osteoporosis).

Up until the 1960s, the ingestion of fluorides from water (whether natural or supplemented) probably represented the bulk of fluoride exposure for both adults and children in most populations (Murray et al., 1991)³. Since then, however, the availability of fluoride from other sources has changed significantly, and fluoride in drinking water is now recognised as just one component of an individual's total fluoride intake. For example, in the 1970s fluoride started to be added to toothpastes and by 1978 96% of toothpaste on the market contained fluoride, usually at a concentration of 1000 to 1500ppm (though it should be noted that in the UK lower fluoride toothpastes containing about 500ppm fluoride are now available for use by children).

The contribution of fluoride in drinking water to total intake varies with the concentration of fluoride in the water. In UK fluoridated areas, drinking water probably remains the most important source of fluoride intake. The relative importance of fluoridated toothpaste as a source of ingested fluoride is greater for young children than for adults because of their greater propensity to swallow it (see section below on fluoride intake in children).

3.3 Biomarkers of fluoride exposure (absorbed dose)

The most important markers of exposure are measured fluoride levels in plasma, urine and bone. Bone provides a measure of cumulative exposure and is probably the best guide to long-term uptake. However it can be difficult to obtain and is not practical for large-scale studies or routine clinical situations. The sampling is invasive and the type/site of bone sampled (usually iliac crest) has to be standardized, as fluoride concentration varies throughout the skeleton. Plasma levels give the best practicable indication of recent fluoride intake; fluoride levels in saliva reflect those in plasma (Jenkins, 1978; Whitford, 1996).

Although a useful marker of absorbed dose, urinary excretion of fluoride is of somewhat limited value for estimating fluoride ingestion because of variation in the proportion of ingested fluoride that is retained, which depends mainly on the level of fluoride intake. For example, in children with low fluoride intake, the proportion that is excreted in the urine is high, and negative balances can occur (see below). A further note of caution on urine fluoride measurement relates to the fact that fluoride excretion is dependent on the pH of the urine. Thus, for example, acidic urine associated with high altitude inhibits fluoride excretion while alkaline urine associated with a vegetarian diet increases fluoride excretion. There also appear to be age-related differences in the proportion of ingested fluoride that is excreted in the urine. Nevertheless, urinary fluoride measurements can be useful markers of recent exposure – especially if 24-hour samples are used – and are particularly valuable in comparative studies of groups of people (eg communities receiving fluoridated water versus those receiving fluoridated salt or milk). They can also be of value in identifying people with probable high fluoride intake, especially if sampling periods of 6 days or more are used.

3 With two exceptions; workers in industries handling fluoride concentrates, and osteoporosis patients given high fluoride doses therapeutically.

Fluoride levels in nails have also been used as a biomarker of fluoride exposure, but are not well standardized against bone or plasma concentrations. Nail fluoride level reflects intake about three to six months before.

3.4 Total exposure studies

A number of studies have attempted to estimate the mean daily intake of fluoride, using a variety of techniques⁴. Most have found intakes of 0.01 to 0.13 mg/kg bw, with most mean intake values between 0.03 and 0.04 mg/kg bw in non-fluoridated areas and 0.04 to 0.06 mg/kg bw in fluoridated areas. However, several studies have found considerable variation, especially in children among whom individual intakes may far exceed the mean value, owing to ingestion of dentifrice, for example (Warren & Levy, 1999).

Table 2 presents an example estimate of daily fluoride intake for adults and children, adapted from Hamilton (1992).

Table 2: Daily fluoride consumption from drinking water, tooth brushing and diet

Source	Concentration/Content	Intake (mg/kg bw) ^a	
		Child	Adult
Drinking water ^b	1.2 mg/l	0.084	0.034
Tooth-brushing and mouth washing	0.145-0.66 mg	0.033	0.002
Diet	0.2-0.4 mg	0.010	0.006
Total intake		0.127	0.042

a Assuming child and adult weights of 20 and 70kg, respectively, together with 100% absorption.

b Assumes child and adult water consumption of 1.4 and 2.0 l/day (likely to be an overestimate for the present day).

Adapted from Hamilton, 1992.

Estimates of fluoride intake by children and adults in fluoridated and non-fluoridated areas have been made by the Australian National Health and Medical Research Council (NHMRC, 1999). They compared the optimal total daily intake of fluoride recommended by the American Academy of Paediatrics (0.05-0.07 mg/kg bw) with estimates of intakes in fluoridated and non-fluoridated areas. The conclusions of the NHMRC were that breast-fed infants under six months in fluoridated and non-fluoridated areas are likely to have 'sub-optimal' intakes of fluoride. The same is true of breast-fed infants of any age in fluoridated areas, who do not use fluoridated toothpaste. Individuals most likely to have supra-optimal fluoride intakes are formula-fed infants in fluoridated areas, infants in non-fluoridated areas fed on high fluoride containing formula, and individuals with excessive toothpaste use and ingestion.

The various available methods for estimating fluoride ingestion have their own particular qualities concerning difficulty and accuracy. Methodological considerations are therefore most important when evaluating and interpreting results from studies of fluoride ingestion, particularly with regard to sample size and measurement period because of individual and temporal variability in intake⁵. Estimates of fluoride ingested from all sources are likely to be imprecise owing to the variation in individual consumption patterns and the differing concentrations of fluoride in foods and beverages. Accurately quantifying fluoride intake from current and past use of water⁶, food, and toothpaste, etc., together with

4 Various methods are available for estimating fluoride ingestion, including retrospective questionnaires, diet diaries, market basket surveys and the "duplicate plate" method.

5 There is a tendency to misinterpret extreme values (for fluoride intake or excretion, for example) from epidemiological surveys; typically, the highest and lowest values recorded are highlighted without regard to the method used to obtain these values. Often one-day records (or worse - less than one day samples) are obtained and presented as the variability between subjects in a population. This ignores intra-subject variation and therefore overestimates the range of intake between individuals.

6 Tap water intake, especially by children, is commonly grossly overestimated. Rugg-Gunn et al. (1987) showed tap water intake (all sources) to be just 616g (0.616l)/day on average (cf estimate by Hamilton, 1992, of 1.4l/day). Because of variability in intake, an averaging sampling period of at least 6 days is recommended (Rugg-Gunn, 1987).

past intake from supplements or infant formula, is certainly very difficult and such estimates must therefore be treated with caution.

3.5 Further information on fluoride intake and excretion in children

The annex (page 44) gives design details and key results from a number of important studies on fluoride intake and excretion in children, together with the authors' conclusions. Various methods were used to measure excretion, but all but one study quoted here used duplicate diet collection for the intake estimates.

The results confirm that some children may be in negative fluoride balance (Ekstrand et al., 1984). This was found to be the case for breast-fed babies, in contrast with formula-fed babies who retained between 52 and 61% of the range of 891 to 1012 mg they consumed per day. In New Zealand in children aged 11 to 13 months the mean intake was found to be 0.028 mgF/kg bodyweight in a fluoridated area and 0.009 mgF/kg bw in a non-fluoridated area. When toothpaste was added the figures were 0.033 and 0.02 mgF/kg bw. The authors concluded that the intakes were within recommended limits although some children might be pushed above these if they used excessive amounts of toothpaste or supplements (Chowdhury et al., 1990). Another study by the same principal author found similar results in older children (Guha-Chowdhury et al., 1996). A study conducted in Japan, where there was very limited access to any fluoridated products but a potentially higher dietary fluoride level, found intakes to be between those of Americans living in fluoridated and in non-fluoridated areas (Kimura et al., 2001). No study produced evidence to suggest that any group was consuming too much fluoride, although Rojas-Sanchez et al. (1999) have cautioned that attention needs to be given to the daily intake of fluoride by young children in both fluoridated and non-fluoridated areas to prevent them being put at risk of developing dental fluorosis.

With regard to excretion, a detailed study by Villa et al. (2000) reported that the proportions of ingested fluoride excreted varied between 24.4% and 62.6%, with a mean of 35.5%. This study was undertaken in an orphanage and the diet of all the children was relatively similar, so the variation in excretion is particularly interesting.

Results of two large studies on both children and adults, to be published shortly, are expected to provide important information on urinary fluoride excretion and allow further improved estimates of total exposure to be made.

3.6 Gaps in the evidence

Research into the health effects of fluorides, driven by public health interest in the artificial fluoridation of water, has hitherto centred almost entirely on the fluorides ingested from water, and there is therefore considerable information regarding the impact of water fluorides on the general population, usually without regard to other sources. Smaller bodies of research have focused on workers in industries handling fluoride concentrates and osteoporosis patients given high fluoride doses therapeutically. Data from such high-exposure situations, in which normal domestic fluoride intake is dwarfed, provide useful information on the relation between fluoride intake and accumulation in bone, at least at high levels of exposure. Estimates of total dietary fluoride intake for the normal population have generally been made by applying mean fluoride concentrations in foodstuffs to food consumption data from periodic nutritional surveys.

As previously recounted, developments since 1960 have altered the general pattern of fluoride exposure and may have created a new situation in the population at large, both with respect to total exposure and the main sources of exposure. There are therefore several deficiencies in the existing body of evidence when evaluating effects relating to fluoride exposure, and other questions that need to be addressed:

The effects of fluorides are probably related to total exposure, not just fluoride in drinking water. There are very few data relating total fluoride exposure to health effects.

Contributions to total exposure by inhalation of airborne pollutants (which can readily be estimated) and trans-dermal absorption from cosmetics and from bathing in fluoridated water are assumed to be small in the general population but have not been quantified empirically.

Estimation of total fluoride exposure by addition of the average intakes from foods, drinks and water may be overlooking important secondary sources.

In addition to mean values and confidence limits, there is a need for frequency distributions of fluoride exposure to enable the identification of individuals or groups exposed to levels considerably higher than the mean. These subgroups could then be the subject of further investigation.

With regard to dental caries and fluorosis, fluoride has a relatively low 'therapeutic ratio' (the ratio between biologically effective dose and toxic dose). There is a need to address the aggregate rate of accumulation of fluoride in target tissues and assess whether this is fast enough to incur the risk of pathology within a reasonable life span in more than a small (and defined) minority of those exposed.

In children, there have been too few studies of total fluoride intake and the contribution of various sources to that intake. The reason has been, largely, because the issue under consideration has been the effect of different levels of fluoride in water, which has usually meant comparisons between areas. Nevertheless, there is a need for further information, especially when linked to fluoride retention and excretion.

Population groups exposed to high levels of fluoride, such as some foundry workers (having increased consumption of fluoridated drinking water) or those employed in aluminium smelters (being occupationally exposed to fluoride), could be studied to address specific questions relating to the risks of high fluoride intake.

A major area of uncertainty concerns the bioavailability of fluoride. This is particularly important with respect to the possible differential absorption of fluoride from naturally and artificially fluoridated water and the role of water hardness (calcium levels).

3.7 Conclusions and research recommendations

In studies of water fluoridation and health, there is potential for confounding or effect modification by sources of fluoride exposure other than water and this needs to be better understood. Questions remain about fluoride bioavailability and also about the most appropriate exposure/dose markers to use in particular studies. It is important to understand the relative importance of different sources of fluoride exposure in children, adults and special occupational groups, and to track trends that occur over time. It is possible that studies of individuals occupationally exposed to fluoride could provide useful additional information on the uptake, absorption, excretion and health effects.

Principal recommendations pertaining to fluoride exposure are as follows:

- New studies are required to investigate the bioavailability and absorption of fluoride from naturally fluoridated and artificially fluoridated drinking water, looking also at the impact of water hardness. This is particularly important because if the bioavailability is the same, many of the findings relating to natural fluoride can also be related to artificial fluoridation.
- Further attempts should be made to calculate lifetime intakes of fluoride, using both urinary and ingestion data, and to determine the relative contribution of fluoride in artificially fluoridated water to total fluoride uptake. If the bioavailability of artificial and natural fluoride were found to be the same, then studies on people who have lived in naturally high fluoride areas could be informative.
- Continuing information is needed on trends in fluoride exposure resulting from changes in the use of discretionary fluorides (eg toothpaste use by infants). The survey of the use of discretionary fluorides by 1.5 to 4.5 year old children included in the National Diet and Nutrition Survey (Hinds & Gregory, 1995) should be repeated.

- If the bioavailability of fluoride from artificially fluoridated water is found to be substantially greater than from naturally fluoridated water, then new studies should address the rate of accumulation of fluoride in target tissues from artificial fluoridation and assess whether this is fast enough to produce a risk of pathological change within a reasonable life span in more than a small (and defined) minority of those exposed.

Within the National Diet and Nutrition Survey, 24 hour urine samples are being collected for fluoride analysis. Additional recommendations for future research will depend to some extent on whether the results are in line with existing estimates of total fluoride intake.

Whatever the outcome it is suggested that:

- Periodic 24 hour urinary fluoride sampling should remain a feature of at least some national diet surveys, to monitor on going trends and particularly to look at fluoride intake across the population.
- Fluoride ingestion (from all sources) and fluoride excretion, and therefore fluoride retention, should be measured in children.
- The relative importance of water as a source of fluoride ingestion in children should be determined.

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4. Principal health outcomes

4.1 Dental caries

The York Review (NHS CRD, 2000) focused particularly on the effects of fluoride on dental caries. The review found that water fluoridation was effective in reducing dental caries, and that the reduction in dental caries experience is greater in those areas with higher levels of dental caries prior to water fluoridation. The change in the prevalence of dental caries was an estimated 15% increase in the proportion of subjects with no dental caries and a decrease of 2.2 in the mean number of decayed, missing or filled teeth (dmft/DMFT)⁷. However, due to the variability between reported studies it was not possible to be precise about the size of these effects. In particular, many studies had failed to take sufficient account of confounding factors. The only two studies that were designed as true cohort studies were not included in the meta-regression analysis because they used different outcome measures from the other studies.

In considering the effects on dental caries the York Review looked only at those studies presenting baseline and follow-up data for both fluoridated and non-fluoridated communities. Furthermore, it considered only two outcome measures: differences in percentages of caries free children, and absolute differences in caries experience (ie differences in dmft/DMFT). The York Review did not consider all studies or all possible outcome measures relating to dental caries; for example it did not include:

- outcome measures such as the percentage of children with high dmft/DMFT, extracted teeth, experience of general anaesthesia for dental extraction, toothache, and point prevalence of dental abscesses;
- cross-sectional studies (for social class analysis) - including important studies on dental caries in adults; or
- long term dental effects in communities with naturally fluoridated drinking water..

4.1.1 Relevant studies

Other reported studies, such as cross-sectional studies conducted in the UK between 1980 and 1990, have shown reductions in dental caries due to fluoride of the same order of magnitude as those reported in the York Review (Rugg-Gunn et al., 1977; French et al., 1984; Duxbury et al., 1987; Mitropoulos et al., 1988; Rugg-Gunn et al., 1988; Carmichael et al., 1989; Seaman et al., 1989). These studies also reported additional effects, such as reductions in the prevalence of both toothache and dental treatment needing general anaesthesia.

In addition, studies have found a reduction in dental caries by water fluoridation in children as young as 3 years of age (Booth et al, 1992) and in adults (Murray, 1971; Newbrun, 1989; Thomas & Kassab, 1992; O'Mulane & Whelton, 1992), even up to 75 years of age (Hunt et al., 1989). Water fluoridation has an important post-eruptive topical effect; a study by Hardwick et al. (1982) found that children aged 12 years at the initiation of fluoridation showed significant benefits within three to four years.

It should be noted that there is difficulty in accurately measuring and predicting the beneficial effects of fluoridation. For example, fluoride may be incorporated into some foods and drinks manufactured in a fluoridated area and subsequently transported to and consumed by residents in a non-fluoridated area. This has the effect of reducing the observed differences in dental caries between fluoridated and non-fluoridated communities, which may cause an underestimation of the benefits of water fluoridation (Griffin et al., 2001). Furthermore, many epidemiological studies have recorded only frank carious lesions and are therefore likely to have underestimated the true prevalence of disease (Pitts & Fyffe, 1988).

4.1.2 Implications

The reduction in sugar consumption in UK children since the 1960s and the introduction of fluoride toothpaste in the 1970s led to substantial reductions in dental caries (Todd & Dodd, 1985). However, these reductions were not uniform and led to widening social inequalities in children's dental health.

⁷ dmft: mean number of decayed, missing or filled teeth in the deciduous dentition (first teeth)
DMFT: mean number of decayed, missing or filled teeth in the permanent dentition

Minority ethnic groups, particularly young children of Muslim non-English speaking mothers, have been shown to be at particularly high risk. Inequalities persist into adult life and are not improving over time (Kelly et al., 2000). The British Dental Association has suggested that water fluoridation should be targeted to high risk communities in order to try to reduce the widespread geographical and social inequalities in dental health.

A report by the York Health Economics Consortium (Sanderson, 1998) commented that the effectiveness of water fluoridation would depend upon the baseline level of caries, and that the capital costs were sensitive to economies of scale. This report suggested that water fluoridation should be targeted at those districts with mean dmft at age 5 years greater than 2.0 and with water supply schemes covering around 200,000 residents.

4.1.3 Research recommendations

The York Review concluded that water fluoridation was effective, but the authors were reluctant to estimate the likely impact in today's environment. Therefore, to inform policy, future research - including economic evaluation - should determine the short-term impacts of water fluoridation on dental caries (ie within 4 years of implementation), though there would be advantages in extending studies to 10 years and beyond in order to capture more fully the effects on the permanent dentition.

Specific recommendations are as follows:

- Further studies (eg prospective intervention studies) are needed in population groups with higher levels of dental caries that i) provide an estimate of the effect of water fluoridation on children aged 3-15 years against a background of widespread use of fluoride dentifrices, and ii) extend knowledge about the effect of water fluoridation by social class (or other relevant measures of socio-economic status) taking into account important potential effect modifiers such as sugar consumption and toothpaste usage.
- Further information is needed on the impact of water fluoridation on recurrent caries in adults and root caries in older adults, controlling for age, social class, ethnic group, sugar consumption and use of discretionary fluorides.
- There is a need to extend understanding of the impact of fluoridation on quality of life and economic indices, in addition to the more customary outcome measures based on the extent of decayed, missing and filled teeth.

4.2 Dental fluorosis

Dental fluorosis is a form of developmental defect of tooth enamel. Histologically it presents as a hypocalcification, while clinically it ranges from barely visible white striations on the teeth through to gross defects and staining of the enamel. There are around 90 different causes of enamel defects of which three or four causes are common. Differential diagnosis is not straightforward, and therefore in epidemiological studies, inter- and intra-examiner variability remains a problem. Minor forms of dental fluorosis are not aesthetically troublesome and may even enhance the appearance of dental enamel (Hawley et al., 1996).

The York Review identified 88 studies (mainly cross-sectional) investigating dental fluorosis, from 30 countries, which suggested a prevalence (all levels of severity) of 48% in fluoridated areas and 15% in non-fluoridated areas. Limiting consideration to aesthetically important levels of severity, the York Review reported the prevalence of fluorosis to be 12.5% in fluoridated areas and 6.3% in non-fluoridated areas. For any given fluoride concentration in water the prevalence of aesthetically important dental fluorosis was higher in naturally fluoridated areas than in artificially fluoridated areas. A sensitivity analysis excluding data points above 1.5ppm fluoride found prevalences for all levels of severity of 46% and 18% and for aesthetically important dental fluorosis of 10% and 6% in fluoridated and non-fluoridated areas respectively. The York Review suggested that there was a dose-response relationship and that most studies failed to take full account of confounding factors. However, the York Review included studies in countries with hotter climates than the UK: in hot climates, water intake is typically higher than in the UK and the risk of fluorosis correspondingly greater for any given water fluoride concentration (Murray, 1986).

4.2.1 Relevant studies

In the UK, the prevalence of aesthetically important dental fluorosis is probably lower than that reported in the York Review. For example, a study by Tabari et al., (2000) found prevalence of fluorosis (in upper permanent incisor teeth) to be 3% in fluoridated Newcastle and 0.5% in non-fluoridated Northumberland. An EU BIOMED funded study (O'Mullane et al., 1999) reported the prevalence of aesthetically important fluorosis (based on photographic diagnosis) in seven European countries, including the UK. Results are reported in Table 3. Only in Cork was the drinking water artificially fluoridated.

Table 3: Prevalence of aesthetically important fluorosis in seven European countries

	Number of children photographed	Prevalence of aesthetically important fluorosis (TF ^a)
Cork (Ireland) Fluoridated	325	4%
Knowsley (UK)	314	1%
Haarlem (Netherlands)	303	4%
Athens (Greece)	283	0%
Almada (Portugal)	210	1%
Reykjavik (Iceland)	296	1%
Oulu (Finland)	315	0%

^a The 'TF' index of dental fluorosis is named after Thylstrup and Fejerskov who developed it (Thylstrup & Fejerskov, 1978)

Source: EU BIOMED study, report to EU dated July 1999 (O'Mullane et al., 1999)

The British Society for Paediatric Dentistry has published guidelines that indicate that discretionary fluorides are an important aetiological factor for dental fluorosis, and recommends that children at low risk of caries should use a small pea sized amount of lower fluoride toothpaste under parental supervision. Fluoride tablets and drops should not be prescribed routinely (Holt et al, 1996). A National survey for 1½ - 4½ year olds and a recent study in the North East of England both indicated that these recommendations were being heeded by significant numbers of parents (Hinds & Gregory, 1995; Tabari et al., 2000). The latter study found that the use of low fluoride toothpaste in infancy was related to a lower prevalence of dental fluorosis in upper permanent incisor teeth.

A higher incidence of dental fluorosis has been reported in children in the USA compared with the UK. However, studies have suggested that 7 to 36% of children living in fluoridated US communities may also be receiving fluoride supplements inappropriately prescribed by their physician or paediatrician (US Department of Health and Human Services, 2001), which could contribute to the higher prevalence values reported in the international data. In addition, low fluoride toothpastes have not been marketed in the USA.

4.2.2 Research recommendations

There are discrepancies between the dental fluorosis data reported by the York Review and recent data from the UK and Europe (detailed above). The public's awareness and understanding of fluorosis is, in general, low. Any future research should aim to provide further understanding of both these two aspects. Further methodological work is needed to validate the Thylstrup-Fejerskov (TF) index of dental fluorosis using histological appearance as the validating criterion.

Specific recommendations are as follows:

- Cross-sectional studies to determine the current prevalence of dental fluorosis in fluoridated and non-fluoridated communities. Photographic techniques are recommended, with careful attention to examiner training, calibration and blinding. Due regard should be given to potential confounding factors and/or effect modifiers such as social class, ethnic group and the use of discretionary fluorides.
- Further studies should determine the public's perception of dental fluorosis with particular attention to the distinction between acceptable and aesthetically unacceptable fluorosis.
- Any prospective epidemiological studies of fluoridation and dental caries should incorporate dental fluorosis as one of the outcome measures.

4.3 Effects of social class

As for many diseases in the UK, dental caries is more prevalent in the more deprived social groups than in more affluent social groups (Beal, 1986). This is especially marked in the primary dentition of young children. High prevalences of toothache, abscesses and dental extractions needing general anaesthesia are associated with the high caries experience recorded in children in deprived social groups in the UK (Rugg-Gunn et al., 1977; O'Brien, 1994; Hinds & Gregory, 1995). The two principal factors influencing dental caries are diet and the use of fluoridated dental care products (especially toothpaste). Diets of more socially deprived children are more caries conducive than diets of more affluent children, and more affluent children brush their teeth with a fluoride toothpaste more often than do more socially deprived children (Hinds & Gregory, 1995).

Water fluoridation has advantages over other possible caries preventive measures in that it reaches everyone in a community who is on a public water supply. It is therefore seen as an equitable public health measure, and there has been considerable interest in the question of whether water fluoridation benefits most those people at greatest risk of dental caries, ie the more deprived members of a community. If so, water fluoridation could be an important means of reducing inequalities in oral health.

This issue was examined in Chapter 6 of the York Review. That report identified and examined results of fifteen studies, published between 1969 and 1999, investigating the associations between water fluoridation, dental caries and social class. The search was limited to the UK – one study was conducted in Wales, the remainder in England. The Review commented that the number of studies in the UK (fifteen) was very small and that the quality of the evidence from the studies was low – all but four were classed as quality level C, the remainder being level B⁸. In the majority of studies, children were classed socially using the UK Registrar General's classification. For these analyses, two measures of dental caries were used – the percentage of children caries free (the reverse of caries prevalence) and mean dmft/DMFT.

Although there was no evidence that water fluoridation reduced the caries prevalence/social class gradient overall, the York Review did find some evidence that water fluoridation reduces inequalities in dental health across the social classes in 5 and 12 year old children, using the dmft/DMFT measure. This effect was not seen in the proportion of caries free 5 year olds. There were insufficient data for the other age groups to be assessed. Regression analyses in two studies (which used methods other than the Registrar General's system for classifying children socially) indicated that children in the more deprived areas achieved greater reductions in tooth decay than children in less deprived areas.

The York Review concluded that there appears to be evidence that water fluoridation reduces the inequalities of dental health across the social classes in five and twelve year olds, using the dmft/DMFT measure. This effect was not seen in the proportion of caries free children among five year olds; the data on caries prevalence in children of other ages also did not demonstrate an effect. The Review suggested caution in interpreting these results because of the small quantity of studies, differences between the studies, and their low quality rating.

A number of authoritative reports have commented on this issue. When discussing inequalities in health in the UK, Acheson (1998) said, "Fluoridation of the public water supply has been shown to reduce dental caries, especially amongst socially deprived communities in the UK and Australia. Water fluoridation provides benefits for everyone but the effects are more pronounced in people in lower social classes, particularly in the primary dentition". In a report to the Canadian Health Ministry, Locker (1999) said "Moreover, the absolute differences in dmft/s or DMFT/S⁹ scores between populations living in fluoridated and non-fluoridated communities is consistently larger in lower socio-economic status (SES) children than in higher SES children. Expressed another way, the difference in caries rates between children from the upper and lower SES groups is narrower in fluoridated than in non-fluoridated communities. This points to an additive interaction between water fluoridation and SES. However, the

8 See York Review page 5. Level B is defined as evidence of moderate quality, level C as evidence of lowest quality.

9 s or S refers to surfaces rather than teeth (t/T)

magnitude of this effect is more pronounced in the deciduous dentition and is generally small". A recent report of the US Centers for Disease Control and Prevention, stated that "Water fluoridation also reduces the disparities in caries experience among poor and non-poor children... Thus, these persons might receive more benefit from fluoridated community water than persons from high SES strata" (US Department of Health and Human Services, 2001).

While higher caries experience in more deprived communities is a common finding in developed countries, this is not so in less well-developed countries. Studies in West Africa, for example, have reported higher caries experience in children from affluent families (due to their ability to purchase high sugar snack foods and drinks; Olojugba & Lennon, 1990). In the UAE, dental caries experience of children was positively related to parental income, but negatively related to parental education (Al-Hosani & Rugg-Gunn, 1998).

4.3.2 Studies conducted outside the UK

Because of the limited data available in the UK to investigate whether water fluoridation reduces social inequalities in dental health, a search was made for studies conducted outside the UK. For reasons alluded to above, this search was limited to the USA, Canada, Europe, Australia and New Zealand. Two studies were located in Australia, five in New Zealand and two in Finland. These nine studies are reviewed below, together with a study validity assessment grade based on the York Review criteria (see Appendix D of the York Review for details). As with the UK studies, the quality of studies was low: all nine studies were graded as 'C' level. No prospective studies were identified.

Brown et al. (1990) reported on the caries experience of eight-year-old children in fluoridated Melbourne and non-fluoridated Geelong, Australia. The results indicated that water fluoridation was able to reduce some of the influence of social class on dmft. [Validity score = 1.0]

Slade et al. (1996) described a study of caries experience of 6,704 Queensland children aged five to twelve years old and 6,814 South Australia children aged five to fifteen years old. Both areas included children exposed or not exposed to water fluoridation. The authors concluded that 'SES inequalities were more pronounced among children who had no exposure to fluoridated water, most probably because of the higher underlying levels of caries experience of children with no exposure to fluoride in the water. Water fluoridation, therefore, has the dual appeal of reducing caries levels among children and, in doing so, reducing SES inequalities in caries experience'. Substantial additive effects were observed, but the multiplicative effects were weak in this study (Spencer et al. 1996). [Validity score = 1.8]

Evans et al. (1984) reported caries experience of five-year-old children (primary teeth) living in Dunedin, New Zealand, which had fluoridated its drinking water in 1967. Statistically significant differences were reported for the effects of both fluoride and SES in analyses of variance. The absolute difference in caries experience between fluoridated and non-fluoridated areas was very much greater in the low SES groups than in the high SES groups. The small cell size (number of subjects for a sub-group analysis) indicates a need for caution in interpreting the results. [Validity score = 0.8]

Colquhoun (1985) examined the statistics of treatment provided to children in Auckland, which had fluoridated in 1966, and a non-fluoridated area. He reported that fifteen years after water fluoridation began in Auckland, there was still a significant correlation between dental treatment requirements of children and their social class. He concluded that 'What is clear from this study is that in Auckland, New Zealand, levels of child dental health are more related to socio-economic factors than to water fluoridation'. Thus, he dismissed the effectiveness of water fluoridation. [Validity score = 0.8]

Fergusson and Horwood (1986) related social background, water fluoridation and the use of fluoride tablets to caries experience (dmft) of a birth cohort of seven-year-old children in Christchurch, New Zealand. The authors concluded that 'In common with the findings of many other studies, there was an inverse relationship between social background and dental health, with increasing social disadvantage being associated with decreasing dental health. However, this association was not particularly strong and it was estimated that, jointly, variation in social background conditions explained only 4% of variation in

dmft scores'. 'Finally, the results suggest that fluoride tablets, social background and residency in a fluoridated area all had significant effects on dmft scores'. [Validity score = 1.8]

Treasure and Dever (1992) examined 147 children aged five years in fluoridated Ashburton and Dunedin, New Zealand, and 195 children of the same age in non-fluoridated Oamaru and Timaru. The authors reported that 'The children in the fluoridated towns showed only minor variations when caries data were analysed by socio-economic status. In contrast, in the non-fluoridated sample, there was a marked social gradient with less-advantaged children having a higher mean dmft'. [Validity score = 1.0]

Treasure and Dever (1994) recorded the caries experience of fourteen-year-olds (permanent teeth) living in three areas – continuous fluoridation, non-fluoridated and an area that had discontinued fluoridation five years previously. The main effects of SES and water fluoridation were statistically significant. Differences in caries experience between the high and low SES groups were greater in the non-fluoridated than in the fluoridated area. Considerable caution in interpreting these data is necessary, due to small cell sizes. [Validity score = 1.0]

Hausen et al. (1981) reported on a survey of the permanent teeth of 2,778 seven to sixteen year-old children living in fluoridated and non-fluoridated areas of Kuopio County, Finland. They concluded that 'Caries frequency is clearly lowest in children of higher social class in both fluoridated and non-fluoridated areas. Differences between middle and lowest social class are, however, small.... water fluoridation has at least some effect in each social class; the effect is of the same magnitude in all social strata'. [Validity score = 0.8]

Hausen et al. (1982) examined the primary teeth of children aged six to nine-years-old living in fluoridated Kuopio and other non-fluoridated areas of Finland. They concluded that 'Children belonging to the highest social class had the lowest caries experience in the primary dentition in naturally high and low fluoridated areas and possibly in areas with fluoridated piped water. The effect of fluoride was similar in all social classes...in Finland, water fluoridation alone is not sufficient to remove differences between social classes in caries in the primary dentition'. [Validity score = 0.8]

4.3.3 Conclusions and research recommendations

There is almost universal agreement that caries experience of children is related to social class. Overall, the balance of evidence is that an additive effect of social class and water fluoridation exists, although this was not found by Colquhoun (1985), and the effect of social class was weak in the two Finnish studies. In the majority of studies water fluoridation reduced dental caries inequalities between high and low social groups; in no study did water fluoridation increase inequalities.

Further studies should be undertaken to address appropriate measures of social inequalities in relation to water fluoridation, dental caries, dental fluorosis and the role of confounding factors such as tooth-brushing with fluoride toothpaste, use of other fluoride therapeutic agents, non-water dietary fluoride ingestion and dietary sugar ingestion. Any such proposed prospective evaluations of water fluoridation and oral health should study communities with an adequate number of people in a wide range of socially diverse groups, and undertake an evaluation of the effect of water fluoridation on the relation between social inequality and dental caries and dental fluorosis with suitable regard to potential confounding factors.

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5. Other potential health outcomes

5.1 Bone health

The York Review included 29 studies on the relation of fluoride in water to bone health. These covered fractures at various anatomical sites, slipped epiphysis and otosclerosis. Eighteen of the investigations provided data on hip fracture. The validity of the studies was generally assessed as low (mean score 3.4 out of 8; see Appendix D of the York Review for details of the assessment criteria) and all but one were classed to the lowest of the three levels of evidence that had been specified at the start of the review.

A total of 55 estimates for the risk of fracture associated with a fluoride concentration of 1 ppm in water was obtained from 20 studies. The relative risks ranged either side of the null value with a pooled estimate from a univariate meta-regression of 1.00 (95% CI 0.94 – 1.06). However, the authors warn that these figures should be interpreted with caution since multivariate analysis revealed significant heterogeneity between the studies.

Two studies of otosclerosis both suggested a beneficial effect of fluoridation, and in a single investigation of slipped epiphysis, fluoride in water was associated with an increased risk in boys and a reduced risk in girls, neither of which was statistically significant.

5.1.1 Potential risk/population effect

Of the potential effects on bone that have been investigated, hip fracture is the most important in public health terms.

In the York Review, the upper 95% confidence limit for the relative risk of all fractures at a water fluoride concentration of approximately 1 ppm was 1.06. Because of the heterogeneity between studies, this figure is subject to some uncertainty. Furthermore, although it was derived largely from studies of hip fracture, some of the data on which it was based related to fracture at other sites. Taking account of these limitations, a reasonable upper bound (ie worst case estimate) for the relative risk of hip fracture from a water fluoride concentration of 1 ppm would be 1.2 (although it is most likely that there is no impact on risk, and there could even be a protective effect).

A relative risk of 1.2 for hip fracture would imply an increase in the lifetime risk of a woman from 14% to approximately 17%, ie an excess risk over a lifetime of about 3%. In men, who have a lower incidence of hip fracture, the excess lifetime risk would be less than 1%. The crude annual incidence of hip fracture in the UK is approximately 1 per 1000 per year.

The epidemiological data currently available do not allow a useful estimate of the potential impact of fluoridation on bone disorders other than fracture, although the few studies that have been carried out to date do not suggest a problem.

5.1.2 Plausibility of effect

An effect of fluoridation on the risk of fracture, adverse or beneficial, is plausible. Fluoridation of water can increase normal dietary intake of the mineral by some 50%, and about half of the fluoride ingested is taken up by bone. Within the bone, fluoride ions can replace hydroxyl ions in the hydroxyapatite lattice with possible implications for its mechanical properties. In addition, elevation of the fluoride concentration in plasma directly increases osteoblastic differentiation and activity.

In theory, a number of other bone disorders could also be affected by these mechanisms. For example, alterations in the hydroxyapatite lattice might influence the development of otosclerosis.

5.1.3 Exposure issues

Many of the epidemiological studies on fluoride and bone health have only assessed risk in relation to current or recent exposure to fluoridated water. However, given the possible mechanisms for an effect on bone, a more relevant metric is likely to be some index of cumulative exposure. This was explored in

a recent MRC case-control study of hip fracture, which found no elevation of risk with exposures to higher fluoride concentrations over a lifetime (Hillier, 2000). A possible limitation of that study, however, was that the exposure to fluoride was almost all from natural sources in water that also contained high concentrations of calcium. It has been proposed that calcium might reduce the bioavailability of fluoride from the gastrointestinal tract, perhaps through ion-pairing, although the importance of any such effect is uncertain (see also Section 3).

Studies of exposure to fluoride in water (especially long-term exposure) are limited by unavoidable inaccuracies in the assessment of individual differences in water intake and of fluoride intake from other dietary sources. In practice, however, these are unlikely seriously to bias estimates of average risks from fluoridation. In particular, confounding by other sources of fluoride in the diet would only have a major impact if total fluoride intake had an important effect on risk (positive or negative), and at the same time, intake from sources other than water differed substantially between fluoridated and non-fluoridated populations.

5.1.4 Gaps in the evidence

The York Review suggests that the evidence base on fluoride and bone health is weak, but this conclusion may be misleading because the criteria by which studies were classified were not entirely appropriate. As outlined above, any effect of fluoride on bone is likely to derive from cumulative exposures, possibly over a lifetime. However, a prime requirement for classification as high level evidence in the review was that studies should have started within three years of the initiation or discontinuation of fluoridation. Any such studies would not be informative about the long-term risk of bone disorders.

A further limitation of the review was that, in grading the validity of studies, it assigned each study a score of zero or one in relation to a pre-defined checklist of features. This is standard practice in systematic reviews, the aim being to make the assessment as objective as possible. However, it has the drawback that the full implications of any weaknesses in the design or execution of individual studies, and the direction of any resultant biases, are not considered.

A broader consideration of the epidemiological evidence on fluoride and bone health suggests that it is of higher quality than the York Review indicates. At this stage, perhaps the most important gap in knowledge concerns the bioavailability of fluoride from different dietary sources, and in particular the influence, if any, of calcium on uptake of fluoride from drinking water (see also Section 3). If fluoride were shown to be much less completely absorbed from hard than soft water, the absence of an increased risk of fracture in some published studies would be less reassuring.

There are also gaps in the evidence base on bone disorders other than fractures, only a few epidemiological studies having attempted to assess risks for any of these diseases directly. However, the gaps could only be regarded as important if there were good reasons to suspect an effect of fluoridation from our knowledge of biochemistry and toxicology.

5.1.5 Feasibility of research

A study to assess the bioavailability of fluoride (see Section 3) from soft as compared with hard water should not be difficult or expensive. If such a study cast serious doubt on the relevance of negative findings from investigations of fracture in relation to water naturally high in fluoride, useful information might be obtained from a well designed case-control study of hip fracture in a population that included people with long-term exposure to artificially fluoridated soft water and others exposed only to low levels of fluoride in water.

In the absence of differential bioavailability, understanding of the risks of fracture from fluoridation will only be advanced materially by further case-control or cohort studies if they are not only designed to minimise the effects of bias and confounding, but also extremely large. Such an effort could only be justified if the upper bounds on risk derived from current evidence were deemed too high for comfort (or the lower bounds were judged to indicate a potentially important beneficial effect), and if a new study would have sufficient statistical power to achieve the required reduction in uncertainty.

Studies on bone disorders other than fracture could be feasible, particularly if the diseases are relatively common, such as Paget's disease.

5.1.6 Research recommendations

The main priority is for research to establish whether the bioavailability of fluoride differs when it is encountered in artificially fluoridated soft water as compared with hard water that is naturally high in fluoride. If important differences were demonstrated, there would then be a need for a case control study to investigate the relation of hip fractures to long-term consumption of artificially fluoridated water.

Studies of other bone diseases would be feasible, but in the absence of clear a priori toxicological concerns, are of lower priority.

5.2 Cancer

The possibility that fluoridation might increase the risk of developing cancer was raised by a series of reports of experiments in mice (Taylor, 1954; Taylor & Taylor, 1965) and by a report in 1975 purporting to show higher overall cancer mortality rates among the 10 largest US cities that practised water fluoridation than amongst the 10 largest US cities that did not (Burk & Yiamouyiannis, 1975). Neither the results of these early animal experiments nor the report of Burk and Yiamouyiannis have been accepted by subsequent expert reviews (eg IARC, 1982; Knox, 1985), but the important public health implications of the question have stimulated many further investigations.

The early studies looked at the possible association of fluoride with cancers of all types. Particular attention has been given to bone cancer, especially osteosarcoma, because ingested fluoride is concentrated in the bones. Some attention has also been given to cancers of the stomach, kidney and thyroid, because fluoride is usually absorbed in the stomach and can be concentrated in the kidneys and thyroid.

5.2.1 Current evidence

The York systematic review identified 26 studies that met the defined inclusion criteria, although two of these were not included in the main analysis (NHS CRD, 2000). Other reviews have evaluated studies using different criteria, and have generally included more studies in their evaluations. This overview is based on the material presented in the York review and other significant reviews (Knox, 1985; DHHS, 1991; Cook-Mozaffari, 1996; NHMRC, 1999).

i) Human data: ecological studies

The majority of data on the association of fluoridation with cancer rates come from ecological studies. Several studies have analysed data sets from ten fluoridated and ten non-fluoridated cities in the USA (Yiamouyiannis & Burk, 1977; NHMRC, 1999; NHS CRD, 2000). With the exception of the analysis by Yiamouyiannis & Burk, which did not adjust appropriately for sex, age and ethnic group, none of these analyses has suggested that overall cancer mortality rates were positively associated with fluoridation. Similar analyses in other areas in the US, and in the UK and elsewhere, have not shown any differences in total cancer rates between fluoridated and non-fluoridated populations, or between populations with water supplies naturally high or low in fluoride. Some ecological studies have looked specifically at bone cancer or at osteosarcoma, and have not observed any associations with water fluoridation (Hoover et al., 1991; Freni et al., 1992).

The largest ecological study was that of Hoover et al. (1991), which included 125,000 incident cancers and 2.3 million cancer deaths, with follow-up for up to 35 years of fluoridation. This study met the inclusion criteria of the York Review but was not included in the main analysis because it grouped non-fluoridated areas together with areas fluoridated within the most recent five years. In our opinion, this aspect of the analysis by Hoover et al. is appropriate, because it is very unlikely that cancer incidence or mortality would increase enough within five years of fluoridation to affect the results. We also consider that the results of this study are very important for the evaluation of the effects of fluoridation, because the large number of cancers studied produces high power to detect small effects. Hoover et al. singled

out osteosarcomas for detailed analysis and found no relationship with fluoridation. The only cancer site for which there was suggestive evidence of a relationship between incidence rates and duration of fluoridation was renal cancer, but in contrast the mortality data for renal cancer yielded some evidence for an inverse relationship with duration of fluoridation. Overall, Hoover et al. identified no trends in cancer incidence or mortality that could be ascribed to the consumption of fluoridated drinking water.

ii) Human data: analytical studies with data for individuals

There are few studies of this type. Three small case control studies of osteosarcoma have been reviewed by NHMRC (1999); two studies estimated individual exposure to fluoridated water from place of residence (McGuire et al., 1995; Moss et al., 1995), the third also included reported use of fluoride tablets and fluoridated toothpaste (Gelberg et al., 1995). None found an increase in cancer risk to be associated with increased exposure to fluoride. Further data are expected from an extension of the preliminary report of the McGuire et al. (1995) study (Lennon, personal communication).

5.2.2 Data from animal experiments

In 1987, IARC concluded that the few data available were insufficient to allow an evaluation of the carcinogenicity of fluoride to animals. Subsequently, however, concern was raised by the publication of the results from a study of lifetime administration of sodium fluoride to rodents (Bucher et al., 1991). The authors interpreted their results as equivocal evidence of carcinogenicity, based on the findings of 1 osteosarcoma in 50 male rats at a dose of 45 ppm and 3 osteosarcomas among 80 rats at a dose of 79 ppm; no associations between fluoride and osteosarcoma were observed among female rats or among mice.

5.2.3 Evaluation of existing data

Overall, the current evidence does not support the hypothesis that exposure to artificially fluoridated water causes an increase in the risk for cancer in humans. It is too early to see whether there might be an effect after very long exposure (see section 5.2.4 below), but the results available rule out more than a very small effect of artificial fluoridation on cancer risk for up to about 35 years of exposure. Furthermore, studies of cancer rates in relation to variations in naturally occurring fluoride levels provide information on lifetime exposure and the absence of any detectable adverse effects of fluoride in these studies provides a high level of reassurance concerning safety (Knox, 1985).

5.2.4 Risk estimate

The evidence available does not suggest that fluoridation of water increases the risk for cancer in general or for any particular type of cancer, including osteosarcoma. Neither the York Review nor other reviews have calculated a pooled estimate of effect, therefore it is difficult to estimate the maximum increase in risk which is compatible with the available data. For osteosarcoma, the three small case-control studies cannot exclude an increase in risk of the order of twofold for exposure to fluoridated water, but an increase as large as this is not compatible with the ecological data, in particular those analysed by Hoover et al. (1991). In conclusion, although a small increase in cancer risk cannot be excluded, the data do not suggest any increase in risk and in view of the type of data available it does not seem appropriate to estimate the number of cases of cancer that might be caused by fluoridation.

5.2.5 Exposure considerations

i) Duration of exposure

Artificial fluoridation was introduced to selected areas in the 1940s and 1950s. Most of the studies conducted so far have used data on cancers diagnosed up until the 1970s and 1980s. The majority of the information, therefore, relates to whether exposure to artificially fluoridated water for up to about 30 years may alter cancer rates, with some data for up to 35 years. There are examples of other agents that do not substantially increase cancer risk until about 25 years after first exposure, and most cancers occur in old age as a result of the accumulation of a lifetime of exposure to genotoxic and/or growth promoting agents. In view of this, there is a need to continue to monitor cancer rates in artificially fluoridated populations for at least 70 years after fluoridation was introduced. However, it should also be noted that studies of populations using water with naturally high fluoride levels, to which the people

would have been exposed throughout their life, have not given any indication of an increase in cancer risk.

ii) Accurate estimation of total exposure to fluoride

The majority of previous studies have used place of residence as an index of exposure to fluoridated water. However, total exposure to fluoride will depend on the volume of water consumed and on other sources of fluoride such as food, drink and toothpaste (see also Section 3). Assessment of all sources would in theory allow estimation of cancer risk in relation to total fluoride intake, and assessment of the component due to fluoridated water. In practice, however, it may be very difficult to obtain sufficiently accurate measures of intakes from all sources. The use of biomarkers such as toenails could be further investigated (see Feskanich et al., 1998 and Section 3).

5.2.6 Plausibility of effect

Very high levels of fluoride have long been known to be toxic, but the features and consequences characteristic of fluorosis in humans and other animals have not included the occurrence of cancer. Most agents that cause cancer directly do so because they are genotoxic, although some (non-genotoxic) agents can cause or promote cancer by other mechanisms, for example by stimulating cell division.

For fluoride, in vitro genotoxicity data are mostly for doses much higher than those to which humans are exposed. Even at these high doses, genotoxic effects are not always observed (NRC, 1993), and fluoride is consistently negative in the Ames test (DHHS, 1991). Some in vivo studies have shown that fluoride can in some circumstances induce mutations and chromosome aberrations in rodent and human cells. Overall, the evidence available has not established that fluoride is genotoxic in humans, and most of the studies suggest that it is not, but the possibility of some genotoxic effect cannot be excluded (DHHS, 1991; NRC, 1993).

Fluoride can have a mitogenic effect on osteoblasts (Bucher et al., 1991); this could provide a mechanism by which fluoride could increase the risk for osteosarcoma.

5.2.7 Gaps in the evidence

As noted above, there is no evidence yet on the possible effects of exposure to artificially fluoridated water for more than 40 years, and there are very few data relating individual exposure to fluoride from water and other sources with cancer risk.

5.2.8 Feasibility of research

Ecological analyses are feasible and should continue for the purpose of looking for possible effects of lifetime exposure to artificially fluoridated water.

More detailed information could be collected on a case-control basis, and might include estimates of total water consumption, other important dietary sources such as tea, and use of toothpaste, plus biomarkers such as toenails (Feskanich et al., 1998). Methodological studies would be needed to develop appropriate methods and to validate their accuracy.

Osteosarcoma is of interest but difficult to study because it is rare, and is not categorised separately in routine statistics. In England and Wales, there were 372 incident cases of bone cancer in 1994, and 204 deaths. Assuming that 34% of bone cancers are osteosarcomas (Hoover et al., 1991, cited in Cook-Mozaffari, 1996), this gives about 125 cases per year.

5.2.9 Research recommendations

I. An updated analysis of ecological data in the UK on fluoridation and cancer rates is required. It would be relatively straightforward to analyse recent cancer incidence and mortality data from ONS in relation to residence in fluoridated areas. Comparisons could be made between similar cities, and data on potentially confounding variables might also be incorporated. The long period since fluoridation

began would give a new analysis the possibility to detect any effect on cancer rates after long exposure.

2. The aetiology of osteosarcoma is poorly understood. If new case control studies of osteosarcoma are undertaken, exposure to fluoride should be included along with the other possible risk factors investigated.

5.3 Other health effects

Fluoride exposure has been postulated to cause a number of health effects other than those described above. Many of these, although plausible, have not been substantiated. The following paragraphs provide a brief summary of the most important of these possible effects, together with recommendations for further work (if any).

5.3.1 Immunological effects

Information regarding the allergic potential of fluoride in drinking water is sparse. A paper by Spittle (1993) concluded that some individuals exhibit an allergic/hypersensitivity reaction to fluoride, but reviews by NRC (1993), NHMRC (1991), and Chalacombe (1996) all concluded that the studies undertaken do not support claims that fluoride is allergenic. They considered the weight of evidence to show that fluoride is unlikely to produce hypersensitivity or other immunological effects. There is no information on the immunotoxicity of fluoride. Further work in this area would be useful, but in the absence of obvious toxic mechanisms for such an effect is considered to be of low priority.

5.3.2 Effects on reproduction

Adverse effects of fluoride intake on reproductive performance, such as reduced lactation, have been demonstrated in many species. However, these studies have used dietary concentrations very much higher than those in the fluoridated drinking water of humans (NRC, 1993).

Fluoride has also been implicated in a number of adverse outcomes relating to fertility and pregnancy, but there is insufficient evidence to establish a link between decreased fertility and fluoride exposure (NHMRC, 1999). The York Review found no evidence of reproductive toxicity in humans (NHS CRD, 2000).

A recent multigenerational study of sodium fluoride in rats, at fluoride levels in drinking water of up to 250ppm, found no impacts on reproduction, and mating fertility and survival indices were not affected (Collins et al., 2001). Parallel studies using the same exposure regimen revealed no evidence for effects on testis structure, spermatogenesis or endocrine function in male rats (Sprando et al., 1997, 1998), nor on numbers of corpora lutea, implants and viable fetuses in females (Collins et al., 2000).

The plausibility of fluoride affecting the reproductive capacity of humans at the intakes experienced from fluoridated drinking water is low.

5.3.3 Birth defects

Fluoride crosses the placenta and is incorporated in the tissues of the developing conceptus. Studies in areas of India and Africa that have high levels of naturally fluoridated water have not shown an increase in birth defects (DHSS, 1991). Erickson et al. (1976) found an association between drinking fluoridated water and congenital malformations in one set of data, but not in another. A study in Atlanta, Georgia, using the birth defects registry, found no association between birth defects and fluoridation of community water supplies (DHSS, 1991).

In 1957, an investigator linked an excess of Down's syndrome to fluoridation. However, later studies by other investigators provided strong evidence against this suggestion (DHSS, 1991; NHS CRD, 2000). The York Review (NHS CRD, 2000) reported six studies that examined whether there is an association between Down's syndrome and drinking water fluoride level¹⁰. All of the studies were of poor quality according to the review criteria. Four of the studies (Berry, 1958; Erickson et al., 1976; 1980; Needleman, 1974) showed no significant association. Two studies (Rapaport, 1957; 1963) found a significant ($p < 0.05$)

positive association, ie increased Down's syndrome incidence with increased water fluoride level. However, it was noted that these two positive studies had methodological limitations; for example they did not control appropriately for the possible confounding effects of maternal age. Other confounding factors not controlled for in most of the studies were incidence of termination of pregnancy in which the child is diagnosed with Down's syndrome, and exposure of the mother to other sources of fluoride. Thus the evidence for an association between water fluoride level and the incidence of Down's syndrome is inconclusive, a conclusion reiterated by Whiting et al. (2001).

If fluoride reaches the developing fetus and is incorporated into its tissues, it could plausibly be teratogenic. The DHSS (1991) review concluded that experimental animal data do not provide any additional evidence for an association between fluoride in drinking water and birth defects; the other major reviews (NHMRC 1991, 1999; NRC, 1993) provide no comment on this issue. A recent multigeneration developmental toxicity study on rats given up to 250ppm fluoride in drinking water (Collins et al., 2000) showed no effects on fetal morphological development, although ossification of the hyoid bone in F2 fetuses was significantly reduced at the 250ppm top dose level.

Human and experimental animal data suggest that drinking even high levels of fluoride in water does not cause birth defects, though there may be adverse consequences for bone ossification at very high exposure levels. Further work on this aspect is not considered to be of high priority.

5.3.4 Renal effects

The kidney is a potential site of acute fluoride toxicity because of its exposure to relatively high fluoride concentrations (NRC, 1993). It has been established from human studies that the kidney removes fluoride from the blood more efficiently than it removes other halides. In addition, renal clearance of fluoride decreases in individuals with renal insufficiency or diabetes mellitus. However, several large community-based epidemiological studies found no increased renal disease associated with long term exposure to drinking water with fluoride concentrations of up to 8mg/l (DHSS, 1991; NRC, 1993).

It is plausible that the kidney could be a target for fluoride toxicity, and there is limited evidence for kidney effects in experimental toxicity studies in animals. Further investigation is therefore warranted to determine the level of toxicity, if any, following low level intakes in humans. However, in view of the negative results in the epidemiological studies mentioned above, this is not considered to be of high priority.

5.3.5 Gastrointestinal tract

With the exception of monofluorophosphate, high concentrations of fluoride releasing compounds form hydrogen fluoride on mixing with hydrochloric acid in the stomach. Hydrogen fluoride can be irritating to the gastric mucosa, resulting in dose-dependent adverse effects. The data for human effects at low exposure are limited, but the indication is that gastrointestinal effects are not a problem at optimal drinking water fluoride concentrations (DHSS, 1991; NRC, 1993).

A study by Susheela et al. (1993) assessed the prevalence and severity of gastrointestinal disturbances (and other non-skeletal manifestations) in an area of endemic skeletal and dental fluorosis in India. The highest prevalence (52.4%) of non-ulcer dyspeptic symptoms was found among 288 individuals (69 families) living in a village where the (natural) mean fluoride concentration in the 36 separate water sources was 3.2ppm (range 0.25 to 8.0ppm). Eleven of these water sources were defined by the authors as 'safe' (ie with fluoride levels of 1.0ppm or less). The authors noted that in patients who reverted to 'safe' water, dyspeptic symptoms and complaints disappeared within 2-3 weeks. Other research by Susheela et al., (1992) revealed that the long term ingestion of fluoride by ten patients on sodium fluoride therapy (30mg per day) for otosclerosis was associated with non-ulcer dyspeptic symptoms in eight of the patients (Susheela et al., 1992).

The effects of fluoride on the gastric mucosa have been described in detail by Whitford (1996). Gastric irritation, by release of hydrogen fluoride in the stomach at high doses of fluoride intake, is plausible. However, it is unlikely that sufficient hydrogen fluoride will be released from the low concentrations of fluoride in drinking water in the UK to cause irritation in healthy individuals. It is possible that individuals who have an existing stomach disorder may be susceptible to irritation following ingestion of fluoridated water, but there is no published evidence for this. This issue is considered to be of low priority for further research.

5.3.6 Intelligence

Two Chinese studies have found a positive association between high levels of fluoride in drinking water and reduced children's intelligence/IQ. Confounding factors were dismissed, but their possible influence on the results of the study was not adequately explained by the authors. At lower fluoride concentrations (eg 0.91 ppm), which are more comparable to the levels in fluoridated water in the UK, a reduction in children's IQ was not observed (Lu et al., 2000; Zhao et al., 1996). There is a possible link here with lead toxicity and the impact of fluoride on lead bioavailability (see below).

Further investigation of this aspect is considered to be of low priority.

5.3.7 Thyroid (goitre)

The York Review listed three studies in which goitre was the outcome of interest. Two of these studies (Gedalia & Brand, 1963; Jooste et al., 1999) found no significant association with water fluoride level. The third (Lin et al., 1991) found a significant positive association between combined high fluoride/low iodine levels and goitre. However, because this study looked at combined fluoride/iodine uptakes, and has not been published in a peer reviewed journal, the findings should be treated cautiously. Further work on this aspect is of low priority.

5.3.8 Miscellaneous effects

Several other health outcomes have been postulated as being connected with elevated fluoride intake:

- Effects on the pineal gland
- Senile dementia
- Age at menarche
- Anaemia during pregnancy
- Sudden Infant Death syndrome
- Primary degenerative dementia

Available information on these outcomes is limited and inconclusive. Further targeted research may be warranted, but this is presently of low priority unless and until critical literature reviews are undertaken that demonstrate specific research needs.

5.3.9 Indirect effects of adding fluoride to water

In addition to any direct impact on health resulting from increased uptake of fluoride by the body, it is possible that fluoridation of water supplies could influence health through other mechanisms. In particular it is necessary to give consideration to the possibility of:

- toxicity from other substances added to water as part of the fluoridation process;
- an effect of higher fluoride in water on dietary exposure to toxic metals (eg through leaching of copper from pipework and dissolution of aluminium from cooking pans); or
- an effect of fluoride in drinking water on the uptake/bioavailability or toxicity of metals in the gut.

The importance of these theoretical hazards will depend on the inherent toxicity of the substances concerned and the impact, if any, of fluoridation on the dose of the toxins.

In addition, it is possible for the presence of other substances in water and food to affect the absorption of fluoride (see also Exposure section) and therefore reduce the effectiveness of an intended caries-preventive dose.

5.3.10 Substances added during the fluoridation process

The UK's Water (Fluoridation) Act 1985 allows hexafluorosilicic acid (H_2SiF_6) and disodium hexafluorosilicate (Na_2SiF_6) to be used to increase the fluoride content of water. The published Code of Practice on Technical Aspects of Fluoridation of Water Supplies (DOE, 1987) gives specifications for these substances and states that 'the product... must not contain any mineral or organic substances capable of impairing the health of those drinking water correctly treated with the product'. For H_2SiF_6 , limits are given for a number of possible impurities, including for iron, heavy metals, sulphate, phosphate, and chloride. The specification for Na_2SiF_6 powder requires a minimum of 98% m/m of the pure chemical, and gives maximum limits for impurities, including heavy metals (as lead) and iron. No other substances are allowed to be used in the fluoridation process, other than an anti-caking agent (the identity of which must be disclosed) in the case of Na_2SiF_6 . Synthetic detergents are not permitted.

Thus there is no likelihood, in normal operation, for any fluoridation plants to introduce other compounds into the drinking water supply (other than approved anti-caking agents and any impurities present in the fluoridation chemicals).

It has been suggested that arsenic is introduced into drinking water through the fluoridation process because this element is present as an impurity in fluoride compounds. However, because of the dilution factor, the contribution of arsenic from this source would be extremely small, and in any case there is a standard for the total arsenic level in drinking water.

5.3.11 Dietary exposure to metals

Enhanced leaching of metals from water pipes and cooking utensils can occur if the fluoridation process significantly alters the pH of the water. This can happen in abnormal (accidental) circumstances. For example, incidents in Westby, Wisconsin and New Haven, Connecticut USA, resulting in peak fluoride levels of 150ppm and 51ppm respectively, reduced the pH value of the water and caused copper to be leached from plumbing¹¹.

Studies on the leaching of aluminium from cooking utensils at standard fluoride concentrations in the region of 1ppm have indicated a small (5%) increase in leaching compared to non-fluoridated water (Moody et al, 1990). These studies indicate that aluminium leaching resulting from water fluoridation is not a significant cause for concern.

5.3.12 Effects on bioavailability or toxicity of toxic metals

Aluminium

Aluminium and fluoride are mutually antagonistic in competing for absorption in the gut. Therefore the more fluoride in the diet, the less aluminium is absorbed. At the same time, ingestion of aluminium counteracts dental fluorosis, reducing fluoride stores in teeth and bones. This effect has been demonstrated in experimental animals and humans (Foster, 1993; quoting Navia 1970). Thus fluoride will reduce rather than increase any toxic potential from aluminium in food or water.

Aluminium has been implicated as having an etiological role in Alzheimer's disease. It follows that if absorption of aluminium is reduced by ingestion of fluoride, this condition should be less common in communities with fluoridated drinking water (Foster, 1993; Kraus & Forbes, 1992). A study conducted in South Carolina (Still & Kelly, 1980) did indeed find a significantly lower rate of admission of Alzheimer's disease patients to mental hospitals from the county with the highest level of fluoride in the drinking water than from the two counties in the same state with the lowest levels, though it had significant methodological shortcomings. A later study by Forbes (1997) found an increased incidence of Alzheimer's disease with higher water fluoride levels. In considering this information it must be cautioned that the possible link between aluminium uptake and Alzheimer's disease is by no means established.

¹¹ See <http://www.fluoridealert.org/accidents.htm>

An experimental study (Varner et al., 1998) found that chronic administration of aluminium fluoride or sodium fluoride in the drinking water of rats resulted in distinct morphological alterations in the brain, including effects on neurones and the cerebrovasculature. The authors concluded that further studies of aluminium fluoride and sodium fluoride are needed to establish the relative importance of a variety of potential mechanisms contributing to the observed effects as well as to determine the potential involvement of these agents in neurodegenerative diseases.

Lead

It is generally considered that lead passes across the intestinal mucosa by both passive and active transport. It appears that lead is actively transported by mucosal protein carriers that mediate calcium transport and that calcium can displace lead, although the interactions between lead and calcium metabolism are complex and not well understood. Experimental evidence suggests that dietary calcium deficiency is associated with an increase in the body burden of lead and the susceptibility to lead toxicity during chronic lead ingestion, and that stimulation of the parathyroid and vitamin D endocrine system is associated with an increase in lead and calcium absorption when significant quantities of lead are not consumed (IEH, 1998). The first of these findings implies that if fluoride reduces calcium uptake, then an increase in lead absorption could result. This is plausible because of the strong affinity between calcium and fluoride, but probably occurs only at high calcium concentrations.

Two recent studies (Masters & Coplan, 1999; Masters et al., 2000) have found an association between ingestion of drinking water treated with silicofluorides and elevated blood lead in children. The authors' conclude that silicofluoride agents maintain lead in suspension and/or enhance lead uptake from the gastrointestinal tract, and postulate that fluoridated drinking water indirectly increases lead toxicity, including fetal and early childhood developmental deficits, and IQ learning deficits. They also make a link between the use of silicofluorides in water treatment systems and increased violent crime. However, according to the US EPA there is no substantive evidence to suggest that fluoridation of drinking water with any fluoridating chemical increases the concentration or bioavailability of lead in drinking water via chemical reactions in the plant, the distribution system, the home plumbing system, or the human body itself (Urbansky & Schock, 2000). This appears to be a controversial area and further studies are awaited.

5.3.13 Conclusions

Further research on the possible effects of fluoride on immunological function, reproduction, birth defects, intelligence, the kidney, gastrointestinal tract and thyroid, and other suggested impacts, is considered to be of low priority.

Substances added to drinking water during the fluoridation process (including impurities of the added substances) are unlikely to add any significant toxic potential to the water.

Fluoride in water at normal levels can increase slightly the amount of leaching of aluminium from cooking utensils. High concentrations of fluoride can also result in leaching of copper from pipework. These effects are considered to be of minimal health significance in normal circumstances.

Fluoride appears to reduce the bioavailability of dietary aluminium. The situation with regard to lead is somewhat less clear-cut and may be influenced by calcium status.

Complexities associated with speciation, ionic interactions etc, yield uncertainties in a number of aspects. It is recommended that this area be kept under review.

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6. Conclusions and principal research recommendations

6.1 Conclusions

This report has considered the scope for further research that could help to inform risk management decisions on water fluoridation. Our starting point was the knowledge base that is already established. Much of this was recently reviewed in the report prepared by the York NHS CRD, and we have not attempted to duplicate their work. We have, however, taken account of additional information (eg, on pharmacology and toxicology) that did not fall within the scope of the York Review. Also, in some areas, our interpretation of the strengths and weaknesses of the existing evidence base differs from that of the York group, and we have indicated where this is so. With this background we have attempted to identify researchable uncertainties and gaps in current scientific understanding that could bear importantly on decisions about fluoridation. In doing this we have taken account of the practicality of further studies that might be carried out.

One of the key issues pertaining to water fluoridation is that of exposure. Because of the use of topical health care products (eg toothpaste) containing fluoride and the potential for exposure from a number of other sources, it is especially important to understand better the total exposure that individuals are experiencing. It is also necessary to gain a better understanding of the bioavailability and absorption of fluoride from naturally fluoridated and artificially fluoridated water.

The main health outcomes of interest and relevance (apart from the intended beneficial effects on dental caries) are dental fluorosis, bone health and cancer. With regard to bone health, the possible impact of fluoridation on risk of hip fracture is the most important in public health terms. We have identified a number of important knowledge gaps relating to these health endpoints; our priority recommendations for research to fill these gaps are listed below. Additional health outcomes suggested by some to be associated with fluoride ingestion include immunological effects, reproductive and developmental toxicity, and effects on the kidney and gastrointestinal tract. Other concerns are related to the chemicals that are added during the fluoridation process, and to indirect effects such as increased leaching of lead from pipes and aluminium from cooking utensils and altered bioavailability or toxicity of these substances. The evidence for any significant health effects associated with these factors is, however, considered to be weak and no specific research studies are recommended here.

There is almost universal agreement that tooth decay in children is related to social class. The majority of the research conducted to date indicates that water fluoridation reduces dental caries inequalities between high and low social class groups. Further studies are recommended that look at appropriate measures of social inequalities related to water fluoridation, dental caries and fluorosis and possible confounding factors.

6.2 Research recommendations

The following recommendations outline a programme of research that would substantially increase our understanding of the impacts of water fluoridation on health and facilitate decision making on public health policy in this area.

Total exposure and uptake

1. New studies are needed to investigate the bioavailability and absorption of fluoride from naturally fluoridated and artificially fluoridated drinking water, looking also at the influence of water hardness. This is particularly important because if the bioavailability is the same, many of the findings relating to natural fluoride can also be related to artificial fluoridation (see recommendations 2, 4 & 14).
2. Further attempts should be made to estimate lifetime intakes of fluoride using both urinary excretion (as an exposure marker) and dietary ingestion data, and to determine the relative contribution of fluoride in artificially fluoridated water to total fluoride uptake. If the bioavailability of fluoride from artificially and naturally fluoridated water (see 1 above) is the same, then studies of fluoride accumulation in people who have lived in naturally high fluoride areas could be informative.

3. Continuing information is needed on trends in fluoride exposure resulting from changes in the use of discretionary fluorides (eg use of toothpaste use by infants).
4. If the bioavailability of fluoride from artificially fluoridated water is found to be substantially greater than from naturally fluoridated water (see I above), then new studies should address the aggregate rate of accumulation of fluoride in target tissues from artificial fluoridation and assess whether this is fast enough to produce a risk of pathological change within a reasonable life span in more than a small (and defined) minority of those exposed.
5. Within the National Diet and Nutrition Survey, 24-hour urine samples are being collected for fluoride analysis. It is recommended that:
 - Periodic 24 hour urinary fluoride sampling should remain a feature of at least some national diet surveys, to monitor trends and particularly to look at fluoride intake across the population.
 - Fluoride ingestion (from all sources) and fluoride excretion - and therefore fluoride retention - should be measured in children.
 - The relative importance of water as a source of fluoride ingestion in children should be determined.

Dental caries

6. Studies are needed to provide an estimate of the effects of water fluoridation on children aged 3-15 years against a background of widespread use of fluoride toothpaste, and to extend knowledge about the effect of water fluoridation by social class (or other relevant measures of socioeconomic status), taking into account potentially important effect modifiers such as sugar consumption and toothpaste usage.
7. Further information is required on the impact of water fluoridation on recurrent caries in adults and root caries in older adults.
8. There is a need to extend understanding of the impact of fluoridation on quality of life and economic indices in addition to the more customary outcome measures based on the prevalence of decayed, missing and filled teeth.

Dental fluorosis

9. Cross-sectional studies are required to determine the current prevalence of dental fluorosis in fluoridated and non-fluoridated communities, taking careful account of potential confounding factors and effect modifiers (see also recommendations 6 and 7 above).
10. Further studies are needed to determine the public's perception of dental fluorosis, with particular attention on the distinction between acceptable and aesthetically unacceptable fluorosis.
11. Any prospective epidemiological studies of fluoridation and dental caries should incorporate dental fluorosis as one of the outcome measures (see recommendation 9 above).

Social class

12. Further studies are needed to address appropriate measures of social inequalities in relation to water fluoridation, dental caries, dental fluorosis and the role of confounding factors such as tooth brushing with fluoride toothpaste, other fluoride therapeutic agents, non-water dietary fluoride ingestion and dietary sugar ingestion (see also recommendations 6 and 10 above).

Bone health

13. If research demonstrates important differences in the bioavailability of fluoride according to the nature of water fluoridation and water hardness (see recommendation I above), a case control study should be carried out to investigate the relation of hip fractures to long-term consumption of artificially fluoridated water.

Cancer

15. An updated analysis of UK ecological data on water fluoridation and cancer rates is required.

Annex - Fluoride intake and excretion in children

Author, year	Study population	Study design	Results																																																		
Ekstrand et al, 1994	4 normal term infants, 2 male, 2 female, USA	<p>A cross over design used to study each infant from 1 to 4 times with the 3 regimens. For 11 days before the study and for the 24 hours of the study all infants consumed the same diet. Under 140 days of age infants only consumed formula and after that were allowed certain products. The formula and all products were of known fluoride concentration.</p> <p>3 regimens; A no fluoride supplementation, B 0.25mg fluoride each day given with a feed (immediately before the second feed of the day, C 0.25mg fluoride 3 hours after the first feed of the day. In B and C parents also gave the fluoride supplement for the 11 days before the fluoride balance but not on the day before the balance study.</p> <p>Urine and faeces was collected for a 72 hour period which started at the time of admission for A and on administration of the fluoride for B and C.</p>	<p>31 balance studies were carried out, 11 on Regime A, 8 on B and 12 on C. Age range from 65 to 422 days on first day of study.</p> <p>Mean and SDs in µg/kg/day</p> <table border="1"> <thead> <tr> <th></th> <th>Intake</th> <th>Urine Excrete</th> <th>Faeces excrete</th> <th>Absorb% Retain%</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>20.5 (4.5)</td> <td>15.5 (1.9)</td> <td>2.0 (0.7)</td> <td>90.1 (3.2) 12.5 (13.8)</td> </tr> <tr> <td>B</td> <td>46.0 (5.2)</td> <td>19.2 (2.7)</td> <td>4.9 (4.5)</td> <td>88.9 (10.5) 47.1 (14.7)</td> </tr> <tr> <td>C</td> <td>48.9 (8.1)</td> <td>21.2 (3.2)</td> <td>2.0 (1.0)</td> <td>96.0 (1.8) 52.3 (6.7)</td> </tr> </tbody> </table> <p>Fluoride from Supplement (mean and SD)</p> <table border="1"> <thead> <tr> <th></th> <th>Intake (mg)</th> <th>Retention (%)</th> </tr> </thead> <tbody> <tr> <td>B</td> <td>234 (12)</td> <td>68.1 (14.8)</td> </tr> <tr> <td>C</td> <td>250 (1)</td> <td>73.0 (6.0)</td> </tr> </tbody> </table> <p>The authors found no evidence to support the idea that the timing of the supplementation influenced the amount absorbed.</p>		Intake	Urine Excrete	Faeces excrete	Absorb% Retain%	A	20.5 (4.5)	15.5 (1.9)	2.0 (0.7)	90.1 (3.2) 12.5 (13.8)	B	46.0 (5.2)	19.2 (2.7)	4.9 (4.5)	88.9 (10.5) 47.1 (14.7)	C	48.9 (8.1)	21.2 (3.2)	2.0 (1.0)	96.0 (1.8) 52.3 (6.7)		Intake (mg)	Retention (%)	B	234 (12)	68.1 (14.8)	C	250 (1)	73.0 (6.0)																					
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Kimura et al, 2001	<p>29 children aged 1 to 6 years, 14 boys, 15 girls, water F <0.05ppm, Japan, no fluoride regime</p> <p>Samples collected from:</p> <table border="1"> <tbody> <tr> <td>August</td> <td>29</td> </tr> <tr> <td>November</td> <td>26</td> </tr> <tr> <td>February</td> <td>28</td> </tr> <tr> <td>March</td> <td>27</td> </tr> </tbody> </table>	August	29	November	26	February	28	March	27	<p>24 hour duplicate diet collection for a three day period repeated four times in each of August, November, February and March; parts of food not normally eaten eg bones, skins removed</p> <p>Results are reported as amount of fluoride consumed per day (F mg/day) and as F mg/kg/day. The range of values, mean and standard deviation are given for each age group and the total sample.</p>	<table border="1"> <thead> <tr> <th>Age</th> <th>n</th> <th>F mg/day Range</th> <th>Mean ± SD</th> <th>F mg/kg/day Range</th> <th>Mean ± SD</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>6</td> <td>0.04-1.24</td> <td>0.23 ± 0.023</td> <td>0.004-0.115</td> <td>0.023 ± 0.023</td> </tr> <tr> <td>2</td> <td>5</td> <td>0.10-0.51</td> <td>0.26 ± 0.12</td> <td>0.009-0.049</td> <td>0.021 ± 0.014</td> </tr> <tr> <td>3</td> <td>6</td> <td>0.11-0.70</td> <td>0.25 ± 0.14</td> <td>0.008-0.052</td> <td>0.019 ± 0.011</td> </tr> <tr> <td>4</td> <td>5</td> <td>0.13-0.66</td> <td>0.26 ± 0.13</td> <td>0.008-0.039</td> <td>0.015 ± 0.007</td> </tr> <tr> <td>5,6</td> <td>7</td> <td>0.09-0.72</td> <td>0.37 ± 0.21</td> <td>0.005-0.043</td> <td>0.018 ± 0.011</td> </tr> <tr> <td>Total</td> <td>29</td> <td>0.04-1.24</td> <td>0.28 ± 0.18</td> <td>0.004-0.115</td> <td>0.019 ± 0.014</td> </tr> </tbody> </table> <p>No seasonal variation, authors conclude that there was a higher level of intake than among Americans living in a non-fluoridated area, lower than Americans living in fluoridated area. The daily energy intake was 78% of that recommended by Ministry of Health. Evidence to suggest that the diets were not unrepresentative of the population.</p>	Age	n	F mg/day Range	Mean ± SD	F mg/kg/day Range	Mean ± SD	1	6	0.04-1.24	0.23 ± 0.023	0.004-0.115	0.023 ± 0.023	2	5	0.10-0.51	0.26 ± 0.12	0.009-0.049	0.021 ± 0.014	3	6	0.11-0.70	0.25 ± 0.14	0.008-0.052	0.019 ± 0.011	4	5	0.13-0.66	0.26 ± 0.13	0.008-0.039	0.015 ± 0.007	5,6	7	0.09-0.72	0.37 ± 0.21	0.005-0.043	0.018 ± 0.011	Total	29	0.04-1.24	0.28 ± 0.18	0.004-0.115	0.019 ± 0.014
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Chowdhury et al, 1990	Children aged 11 to 13 months, 65 consented and 60 completed the study, 31 in a fluoridated and 29 in a non-fluoridated area, New Zealand.	<p>Duplicate portion technique was used for a three day period, leftovers and parts not normally consumed were removed.</p> <p>It was noted how children were fed and the use of toothpaste and supplements.</p> <p>Results are presented for each individual and for fluoridated and non-fluoridated areas in mg F/day and mg F/kg bw (body weight). They are presented for food and drink only and all sources of fluoride.</p>	<table border="0"> <tr> <td></td> <td>Fluoridated n=31</td> <td>Non-fluoridated n=29</td> </tr> <tr> <td>Mean</td> <td>SD</td> <td>Range</td> </tr> <tr> <td>Mean</td> <td>SD</td> <td>Range</td> </tr> </table> <p>Food and drinks</p> <table border="0"> <tr> <td>mgF/day</td> <td>0.263</td> <td>0.131</td> <td>0.089-0.549</td> <td>0.082</td> <td>0.054</td> <td>0.038-0.314</td> </tr> <tr> <td>mgF/kg bw</td> <td>0.028</td> <td>0.013</td> <td>0.009-0.056</td> <td>0.009</td> <td>0.006</td> <td>0.004-0.038</td> </tr> </table> <p>From all sources</p> <table border="0"> <tr> <td>mgF/day</td> <td>0.305</td> <td>0.232</td> <td>0.093-1.299</td> <td>0.195</td> <td>0.174</td> <td>0.039-0.720</td> </tr> <tr> <td>mgF/kg bw</td> <td>0.033</td> <td>0.026</td> <td>0.009-0.150</td> <td>0.020</td> <td>0.017</td> <td>0.004-0.061</td> </tr> </table> <p>The authors concluded that the current levels of fluoride intake of the infants studied from food and drink alone are not in excess of recommended optimal levels of intake. They noted that the use of toothpaste and supplements could push some infants above the recommended levels.</p>		Fluoridated n=31	Non-fluoridated n=29	Mean	SD	Range	Mean	SD	Range	mgF/day	0.263	0.131	0.089-0.549	0.082	0.054	0.038-0.314	mgF/kg bw	0.028	0.013	0.009-0.056	0.009	0.006	0.004-0.038	mgF/day	0.305	0.232	0.093-1.299	0.195	0.174	0.039-0.720	mgF/kg bw	0.033	0.026	0.009-0.150	0.020	0.017	0.004-0.061
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Guha-Chowdhury et al, 1996	74 children met the inclusion criteria. Children were selected according to their caries status and fluoridation status. 66 children aged 3 to 4 years, were available for all three examinations. There were thus four cells in the whole study but in this paper the high caries (ds>3) and caries free children (checked by radiograph at baseline) were combined and their fluoride intake presented by area of residence.	24 hour duplicate diets collected on three separate days at intervals of 6 months. Leftovers, skins and bones etc were removed from the analysis and the parents brought the duplicate plate to the clinic. The amount of toothpaste used and swallowed was determined, using a detailed method that involved measuring the fluoride that was spat out and the fluoride that was left on the brush.	<table border="0"> <tr> <td></td> <td>Fluoridated n=34</td> <td>Non-fluoridated n=32</td> </tr> <tr> <td>Range</td> <td>Mean ± SD</td> <td>95%CI</td> </tr> <tr> <td>Range</td> <td>Mean ± SD</td> <td>95% CI</td> </tr> </table> <p>Diet alone</p> <table border="0"> <tr> <td>mgF/day</td> <td>0.05-0.31</td> <td>0.15± 0.06</td> <td>0.13-0.17</td> <td>0.09-0.74</td> <td>0.36± 0.17</td> <td>0.30-0.42</td> </tr> <tr> <td>mgF/kg bw</td> <td>0.004-0.02</td> <td>0.008 ± 0.003</td> <td>0.006-0.010</td> <td>0.004-0.04</td> <td>0.019± 0.009</td> <td>0.015-0.023</td> </tr> </table> <p>Diet and toothpaste</p> <table border="0"> <tr> <td>mgF/day</td> <td>0.17-1.21</td> <td>0.49±0.25</td> <td>0.41-0.57</td> <td>0.26-1.31</td> <td>0.68±0.27</td> <td>0.59-0.77</td> </tr> <tr> <td>mgF/kg bw</td> <td>0.01-0.06</td> <td>0.027±0.012</td> <td>0.023-0.031</td> <td>0.01-0.07</td> <td>0.036±0.015</td> <td>0.030-0.042</td> </tr> </table> <p>The authors concluded that the current levels of fluoride intake of the infants studied from food and drink alone are not in excess of recommended optimal levels of intake. They noted that the use of toothpaste and supplements could push some infants in low fluoridated areas above the recommended levels.</p>		Fluoridated n=34	Non-fluoridated n=32	Range	Mean ± SD	95%CI	Range	Mean ± SD	95% CI	mgF/day	0.05-0.31	0.15± 0.06	0.13-0.17	0.09-0.74	0.36± 0.17	0.30-0.42	mgF/kg bw	0.004-0.02	0.008 ± 0.003	0.006-0.010	0.004-0.04	0.019± 0.009	0.015-0.023	mgF/day	0.17-1.21	0.49±0.25	0.41-0.57	0.26-1.31	0.68±0.27	0.59-0.77	mgF/kg bw	0.01-0.06	0.027±0.012	0.023-0.031	0.01-0.07	0.036±0.015	0.030-0.042
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Ekstrand et al 1984	5 breast fed and 5 bottle fed infants aged 8 to 28 weeks, all living in an area with 1ppm F in the drinking water	All children's fluoride intake and excretion was measured for a 24 hour period. The babies were weighed to calculate how much they had consumed. All urine and faeces were collected.	<p>Breast fed babies Intake Range 5 - 8 mg, urinary output was mean of 30.4mg ± 12.4 (range 15.6mg to 49.7mg) and 1.3mg ± 1.0 in faeces (range 0.1mg to 2.7mg).</p> <p>Bottle fed babies intake range 891 - 1012 mg, urinary output was mean of 359.7mg ± 45.9 (range 265.1mg to 427.1mg) and 22.9mg ± 21.5 in faeces (range 4.8mg to 48.9mg)</p> <p>All the breast fed babies were in negative balance compared with a retention rate of 52 to 61% in the bottle fed group.</p> <p>Data are presented for all as individuals.</p>																														
Brunetti and Newbrun, 1983 abstract only	10 children, (4 boys, 6 girls) aged 3 to 4 years, USA, in fluoridated area 1 ppm	8 Children studied for 4 consecutive days, 1 for 3 consecutive days and 1 twice for 2 consecutive days over a five day period. Duplicate diet collected as were all urine and faeces. Diffusion method of Waterhouse et al (different to other studies).	<p>Average daily intake was 0.33 ± 0.14 mg / day and the excretion was 0.28 ± 0.08 mg / day. The average fluoride daily balance was 0.05 ± 0.08 mg / day.</p> <p>The authors concluded that fluoride retention was minimal.</p>																														
Villa et al, 2000	20 boys aged 3 to 5 years, six or seven of each year of age, living in an orphanage, water fluoride level of 0.05-0.6 ppm and an altitude of 500-700m above sea level. Chile	Assessment made on two consecutive 24 hour periods of intake and excretion of fluoride. Height and weight measures, toothpaste use and swallowing was assessed for each individual. All children ate the same food and it was checked that there were no leftovers. Water consumption was recorded. Duplicate samples were taken. Data presented for individuals	<p>Fluoride intake</p> <table border="1"> <thead> <tr> <th></th> <th>Mean</th> <th>S.D.</th> <th>Range</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>Total mgF</td> <td>1.019</td> <td>0.105</td> <td>0.846-1.176</td> <td>0.973-1.065</td> </tr> <tr> <td>mg F/kg/day</td> <td>0.064</td> <td>0.015</td> <td>0.042-0.093</td> <td>0.057-0.071</td> </tr> </tbody> </table> <p>Fluoride excretion</p> <table border="1"> <thead> <tr> <th></th> <th>Mean</th> <th>SD</th> <th>Range</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>mg/day</td> <td>0.358</td> <td>0.076</td> <td>0.251-0.55</td> <td>0.325-0.391</td> </tr> <tr> <td>% of intake</td> <td>35.5%</td> <td>8.4%</td> <td>24.4-62.6%</td> <td>31.7-39.3%</td> </tr> </tbody> </table> <p>This paper contains a detailed discussion of several factors such as urinary pH.</p>		Mean	S.D.	Range	95% CI	Total mgF	1.019	0.105	0.846-1.176	0.973-1.065	mg F/kg/day	0.064	0.015	0.042-0.093	0.057-0.071		Mean	SD	Range	95% CI	mg/day	0.358	0.076	0.251-0.55	0.325-0.391	% of intake	35.5%	8.4%	24.4-62.6%	31.7-39.3%
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Zohouri and Rugg-Gunn, 2000	Children aged 4, with water fluoride level of 0.30-0.36 ppm, 78 of 116 children completed all aspects of the survey, Iran.	3 day food diaries were collected by interview and food substances checked for fluoride concentration. Ingestion of fluoride from toothbrushing was estimated for each child. 24 hour urine was collected and analysed from each child. The measurements were made once in summer and once in winter for each child. Excretion in faeces was not measured.	<p>Mean figures with SD</p> <p>Fluoride from diet</p> <p>0.390 ± 0.122 mg /day; $0.028 \pm$ mg/kg/day</p> <p>Fluoride from all sources 0.426 ± 0.126 mg/day;</p> <p>Mean urinary excretion 0.339 ± 0.1 mg/day</p> <p>The difference was $+0.087 \pm 0.143$ mg equivalent to 80% excretion</p> <p>Fluoride ingestion was higher in summer and higher in rural areas.</p> <p>The authors concluded that this was a much higher level of excretion that had been reported previously for children in this age group. They hypothesised that it might in part be due to urinary pH as a result of the children's vegetarian diet.</p>

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