

APPENDIX 2

Risks According to “Tier One” Reviews

Introduction

All major “Tier One” and two documents used by the Fort Collins technical study group were scanned for relevant passages, and an effort was made to group these by the potential health outcome so that for each outcome, some of the most thorough completed reviews of the literature were available in one location. In order to keep this appendix to a reasonable size and scope, not all passages from each reference were included. Priority was given to passages that summarized studies that examined the exposure of humans to naturally or adjusted fluoridated water. Because “the dose makes the poison” some studies of human populations exposed to higher doses of fluoride (>1 ppm F) where ill effects were not detected were included. With the exception of some animal cancer data, animal toxicology studies are not included in this appendix. Additionally, some material was judged repetitive of material that was already cited and not included; only summary findings were included of some of the non-tier works where reviews of the literature were less than thorough. Readers are encouraged to check the complete documents for additional information.

Passages from the Agency for Toxic Substances and Disease Registry are from the 2001 Draft for Public Comment, 2001

References cited can be located within the cited document.

Topic: CANCER

Major "Tier One" Reviews (United States, World Health Organization, & York)

Medical Research Council. Medical Research Council working group report: water fluoridation and health. (September 2002).

Pages 29-32: The possibility that fluoridation might increase the risk of developing cancer was raised by a series of reports of reports of experiments in mice (Taylor, 1954; Taylor & Taylor 1965) and by a report in 1975 purporting to show a higher overall cancer mortality rate among the 10 largest US cities that practiced water fluoridation than amongst the 10 largest cities that did not (Burk & Yiamouyiannis, 1975). Neither the results of these early experiments nor the report of Burk & Yiamouyiannis have been accepted by subsequent expert reviews (e.g. 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.

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 material presented in the York review and other significant reviews (Knox, 1985; DHHS, 1991; Cook-Mozaffari, 1996; NHMRC, 1999)

Human data: ecological studies. The majority of data on the association of fluoridation with cancer rates come from ecological studies. Several studies have analyzed 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 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 adverse 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.

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).

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.

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 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).

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 exposure to fluoridated water, but an increase as large as this is not compatible with the ecological data, in particular those analyzed 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.

Exposure considerations:

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.

Accurate estimation of total exposure to fluoride. The majority of previous studies have used place or 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. Assessment of all sources would in theory allow estimation of cancer risk in relations 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).

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.

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.

Feasibility of research. Ecological analyzes 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 categorized 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.

Research recommendations.

1. An updated analysis of ecological data in the UK on fluoridation and cancer rates is required. It would be relatively straightforward to analyze 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.

Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. (2001 draft and 1993). Toxicological profile for fluorides, hydrogen fluoride, and fluorine.

Page 96: Numerous epidemiological studies have examined the issue of a connection between fluoridated water and cancer. The weight of evidence indicates that no such connection exists. However, all of the investigations were ecologic studies, and the sensitivity limit of even the most sensitive analysis in these studies appears to be a 10-20% increase. Since any carcinogenic effect of fluoride at the levels found in water supplies would probably be below this level of sensitivity, a National Toxicology Program (NTP) cancer bioassay was conducted to assess the effect of fluoride on cancer incidence in animals (Bucher et al., 1991; NTP, 1990). The NTP study found equivocal evidence of a fluoride related increase in osteo-sarcomas in male rats, and no evidence of any fluoride-related neoplasm in female rats or male and or female mice. A study sponsored by Proctor & Gamble (Maurer et al., 1990) found no evidence of fluoride carcinogenicity in either male or female rats. Both studies contain limitations that preclude strong conclusions. The NTP study is presently carrying out additional experiments on the relationship, if any, between fluoride and cancer. The International Agency for Research on Cancer (IARC) reviewed the literature on carcinogenicity in 1982. It concluded that there is no evidence from epidemiological studies of an association between fluoride ingestion and human cancer mortality, and the available data are inadequate for an evaluation of the carcinogenicity of sodium fluoride in experimental animals (IARC). Several major cancer bioassays have been conducted since the IARC review.

Page 97: Data suggesting that increased fluoride exposure from drinking water supplies is associated with an increase in cancer incidence come from the study published by Yiamouyiannis and Burk (1977) comparing cancer incidence rates in 10 US cities with artificial fluoridation and 10 cities without fluoridation. The authors of the study interpret the data as showing that cancer mortality was higher in the cities with artificially fluoridated water. Data from this study has been re-analyzed several times in an attempt to further explore the hypothesis that fluoridation of water supplies causes cancer (Chilvers, 1982, 1983; Doll & Kinlen, 1977; Hoover et al., 1976; Kinlen & Doll, 1981; Oldham & Newell, 1977; Taves, 1977). None of these re-analyses provided evidence of a positive association between fluoridation of water supplies and cancer of any of the sites considered. The re-analyses attributed the positive association between fluoride exposure and cancer reported by Yiamouyiannis and Burk (1977) to dissimilarities in age, race, sex, and demographic factors for the populations studied. Other studies of large populations, both in the US and Great Britain have identified no relationship between artificially or naturally occurring fluoride in drinking water and an increase in cancer incidence (Griffith, 1985; Hoover et al., 1991; Kinlen, 1975).

Page 98: An epidemiological study (Hoover et al., 1991) examined >2,300,000 cancer deaths and 125,000 cancer cases in US counties exposed to artificially fluoridated drinking water for up to 35 years. Taking into account the results of the NTP study, detailed analyses were conducted of cancers of the joints and bones (especially osteosarcomas), and cancers of the oral cavity and pharynx. The statistical evaluation was based on analysis of time

trends in the observed/expected (O/E) ratios relative to duration of fluoridation. While elevated O/E ratios were observed for osteosarcomas in males, the O/E ratio was inversely related to duration of fluoridation. Thorough analyses of incidences of oral cancers and cancers at a variety of other sites were conducted by means of very sensitive statistical tests that were designed to detect changes as small as 10-20%. No consistent correlation between cancer incidence or mortality and duration of fluoridation was found. An addendum to the report noted that the age-adjusted national incidence of osteosarcoma increased by 18% in males for the years 1973-80 and 1981-87; most of the increase was due to a 53% increase in males under 20 years of age, and there was a larger increase in fluoridated than nonfluoridated areas. A similar time-trend analysis to that done in the main report found no correlation between the cancer incidence O/E ratio and duration of fluoridation. Additional analyses also failed to find a relationship between osteosarcoma incidence in males and exposure to water fluoridation.

Pages 98-100: Based on the finding of a rare tumor in a tissue known to accumulate fluoride, but not at the usual site for chemically-associated osteosarcomas, a weakly significant dose-related trend, and the lack of supporting data in female rats and mice of either gender, the NTP concluded that there was “equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats.” NTP defined equivocal evidence of carcinogenic activity to be a situation where the results show “a marginal increase in neoplasms that may be chemically related.” NTP further concluded that there was no evidence that fluoride was carcinogenic at doses up to 4.73 mg/kg/day in female N344/N rats, or at doses up to 17.8 and 19.9 mg/kg/day in male and female B6C3F₁ mice, respectively.

Page 100-101: A study sponsored by Proctor and Gamble examined carcinogenic potential of sodium fluoride administered in feed to Sprague-Dawley rats (Maurer et al., 1990). Statistical analysis of the incidence of bone tumors found no dose-response relationship (CDER, 1991). The Carcinogenicity Assessment Committee, Center for Drug Evaluation and Research, Food and Drug Administration (CAC/CDER/FDA) review concluded that there were “flaws and uncertainties in the studies that keep them from providing strongly reassuring data.” However, the committee concluded that the study results reaffirm the negative finding of the NTP study in female rats, and do not reinforce equivocal findings in male rats.

NHS Centre for Reviews and Dissemination, University of York. (2000). [A systematic review of public water fluoridation](#). York, UK: York Publishing Services Ltd.

Page xiii: There were 26 studies of the association of water fluoridation and cancer included. Eighteen of these studies were from the lowest level of evidence (level C) with the highest risk of bias.

There was no clear association between water fluoridation and overall cancer incidence and mortality. This was also true for osteosarcoma and bone/joint cancers. Only two studies considered thyroid cancer and neither found a statistically significant association with water fluoridation.

Overall, no clear association between water fluoridation and incidence or mortality on bone cancers, thyroid cancer or all cancers was found.

Page 58: The evidence of the effect of water fluoridation on cancer was of the highest quality available under objective 4 (3.8 out of 8 compared to a mean of 2.7 for other possible negative effects) but was still only low to moderate. Twenty-one of the 26 studies presented are from the lowest level of evidence (level C) with the highest risk of bias. While prospective study designs may be more difficult to conduct in cancer studies due to long incubation periods and rarity of some cancers, they are possible. Blinding of outcome assessment to exposure is certainly possible in such studies, for example outcomes assessed using published sources could blind investigators to fluoride levels in the study areas.

There is no clear picture of association between water fluoridation and overall cancer incidence and mortality. Whilst there were 11 analyses that found the direction of association of water fluoridation and cancer to be positive (fewer cancers), a further nine analyses found a negative direction of association (more cancers), and two studies found no effect. Only two studies found statistical significance, both suggesting an association in different directions. One of these studies contained 8 analyses of which only 2 found a statistically significant adverse effect of water fluoridation.

While a broad number of cancers were represented in the included studies, osteosarcoma, bone/ joint and thyroid cancers were of particular concern due to fluoride uptake by bone and thyroid. Again, no clear association between water fluoridation and increased incidence or mortality was apparent. Of eight analyses from the six studies of

osteosarcoma and water fluoridation reporting variance data, none found statistically significant differences. Thyroid cancer was also considered but only two studies examined this and neither found a statistically significant association with water fluoride level.

The findings of cancer studies were mixed, with small variations on either side of no effect. Individual cancers examined were bone cancers and thyroid cancer, where once again no clear pattern of association was seen. Overall, from the research evidence presented no association was detected between water fluoridation and mortality from any cancer, or from bone or thyroid cancers specifically.

World Health Organization. (1994). WHO technical report series #846: Report of a WHO expert committee on oral health status and fluoride use. Geneva, Switzerland: World Health Organization.

Page 12: Claims of osteosarcoma induced by fluoride are based on equivocal evidence from studies of rats, which received extremely high amounts of fluoride. The correlation between osteosarcoma and fluoride thus remains unproven. Examination of the medical records of human osteosarcoma, a rare condition, has failed to identify any relationship between osteosarcoma and fluoride history, and other extensive evaluations of available information have failed to find any potential association between fluoride-induced osteosarcoma and fluoride intake in humans.

National Research Council. (1993). Health effects of ingested fluoride. Washington, D.C.: National Academy Press.

Page 10-11: More than 50 epidemiological studies have examined the relation between fluoride concentrations in drinking water and human cancer. Most studies compared geographic or temporal patterns of cancer occurrences with distributions of fluoride in drinking water. These studies provide no credible evidence for an association between fluoride in drinking water and the risk of cancer. The existence of such an extensive epidemiological database on fluoride with no consistent evidence of carcinogenic effects suggests that, if there is any increase in cancer risk due to exposure to fluoride, it is likely to be small. However, most of these studies used geographic and temporal comparisons of cancer rates and hence are of limited sensitivity. Further analytical studies with accurate information on individual fluoride exposures and disease diagnoses are therefore desirable.

The subcommittee also reviewed the literature on the potential carcinogenic effects of fluoride in animals. Although the results of earlier animal studies were largely negative, the studies were not conducted using current bioassay techniques and are thus of limited value. The sub-committee placed greater weight on two recent studies. The first, conducted by the National Toxicology Program (NTP), administered fluoride at concentrations of up to 175mg/L of drinking water. Although the results were negative for male and female mice and female rats, there was some evidence of a dose-related increase in the incidence of osteosarcomas in male rats. However, these results were not confirmed by a second study conducted by Procter & Gamble, in which fluoride was administered in the diet at doses higher than those in the NTP study. The Procter & Gamble study did produce a significant dose-related increase in the incidence of osteomas (benign bone tumors) in male and female mice. However, these lesions were not considered to be neoplastic and, in any event, have no known counterpart in human pathology.

The subcommittee concludes that the available laboratory data are insufficient to demonstrate carcinogenic effects of fluoride in animals. The subcommittee also concludes that the weight of the evidence from the epidemiological studies completed to date does not support the hypothesis of an association between fluoride exposure and increased cancer risk in humans.

The relevant scientific literature has been exhaustively reviewed by several independent expert panels of epidemiologists. The two most comprehensive evaluations were conducted by the British Working Party on the Fluoridation of Water and Cancer under the chairmanship of E.G. Knox (Knox, 1985) and by an international panel of epidemiologists convened by the Monographs Programme of the International Agency for Research on Cancer in Lyon, France (IARC, 1982). The expert panel reviews generally agree that available data provide no credible evidence for an association between either naturally occurring fluoride or added fluoride in drinking water and risk of human cancer. The Knox Report concluded that there is “no reliable evidence of any hazard to man in respect to cancer.” The IARC group (1982) came to a similar conclusion, namely, that “Variations geographically and in time in the fluoride content of water supplies provide no evidence of an association between fluoride ingestion and mortality from cancer in humans.”

Committee to Coordinate Environmental Health and Related Programs, USPHS. (1991). Review of fluoride: Benefits and risks: Report of the subcommittee on fluoride of the EHPC. Public Health Service: Department of Health and Human Services.

Page 3-4 of executive summary: Epidemiologic studies – the subcommittee reviewed the results from numerous epidemiologic studies of the relation between exposure to fluoridated water and cancer that have been conducted during the last 40 years. In addition to the review of these studies, the subcommittee reviewed the findings of a recent study from the National Cancer Institute (NCI), which updated and expanded an earlier county-specific analysis for cancer mortality in the U.S. in relation to water fluoridation. This study evaluated the cancer mortality data and examined patterns of cancer incidence from 1973 through 1987 in the Surveillance, Epidemiology and End Results (SEER) program cancer registries. The SEER registries were used to obtain data on incidence for all types of cancer, with special emphasis on trends in osteosarcomas.

The NCI study identified no trends in cancer risk that could be attributed to the introduction of fluoride into drinking water. There were no substantial differences in cancer mortality rates among persons who lived in counties that had initiated water fluoridation and those in persons who lived in counties without water fluoridation. Similarly, there was no apparent relation between introduction and duration of fluoridation and the incidence of cancer, including bone and joint cancer and the subset of osteosarcomas.

The NCI also conducted a more detailed evaluation of osteosarcomas using nationwide age-adjusted incidence from the entire SEER database for the years 1973-1987. During this time, the annual incidence of osteosarcoma among males <20 years of age increased from 3.6 cases/10⁶ population to 5.5 cases/10⁶ population. The incidence among females decreased slightly during the same period (from 3.8 cases/10⁶ population to 3.7 cases/10⁶ population). Although the increase in rates of osteosarcoma for males during this period was greater in fluoridated than non-fluoridated areas, extensive analyses revealed that these patterns were unrelated to either the introduction or duration of fluoridation. Consequently, the NCI report concluded that, while the explanation for the increase in rates of osteosarcoma among young males is unknown, it is not due to exposure to water fluoridation. Both this report and reports from previous international expert panels which have reviewed earlier data concluded that there is no credible evidence of any association between the risk of cancer and exposure to either natural or adjusted fluoride in drinking water.

Page 4 of executive summary: Animal Studies: The NTP study found that rates of osteosarcomas rose as the dose of sodium fluoride exposure for male rats increased, but not for female rats or for mice of either gender. These findings were interpreted as “equivocal evidence” of carcinogenicity for male rats but no evidence of carcinogenicity for the other gender/species tested. In another recent carcinogenicity study conducted by Maurer, Cheng, Boysen, and Anderson and sponsored by Proctor and Gamble (P&G), no evidence was found for an association between the development of malignant tumors and exposure to sodium fluoride in rodents of either gender. Taken together, the NTP and P & G studies fail to establish an association between fluoride and cancer.

Page 76 of full report: The mouse data from the P & G study can be compared and contrasted with the NTP mouse study data. The NTP study conducted in B6C3F₁ mice at lower doses of fluoride administered in the drinking water showed no evidence of carcinogenicity. The P & G study conducted in CD1 mice at higher doses of fluoride administered via the diet showed osteomas, but was confounded by the type C retrovirus in mice. The NTP mice had few histopathologic effects on bone but definite discoloration of teeth compared with the P & G mice; the latter showed histopathologic bone and teeth effects associated with chronic fluoride toxicity. This difference is consistent with the lower levels of bone fluoride detected in the NTP study, although many different bones were evaluated. No malignant bone tumors associated with fluoride exposure were seen in mice in either study.

In the P & G rat study, 2 osteosarcomas occurred in the 4 mg/kg-BW females and 1 osteosarcoma in the 25 mg/kg-BW males. The incidence in either sex was not statistically significant. One osteosarcoma was identified by P & G in the pre-maxilla of a low-dose female rat (Maurer, 1990). The osteosarcoma in the high-dose male was identified as such by pathologists at the Armed Forces Institute of Pathology (AFIP) and this diagnosis is the subject of divided expert opinion (FDA, 1990). No agreement has been reached regarding this discrepancy; however CAC and this subcommittee opted to use the “worst case scenario” in interpreting the data and therefore considers the results to encompass two osteosarcomas in 4-mg/kg-BW female rats, one osteosarcoma in a 25 mg/kg-BW male rat, and one fibroblastic sarcoma in the 175 ppm sodium fluoride male rat. In the NTP study researchers found 3 osteosarcomas in the 175ppm sodium fluoride male rats (8.6 mg/kg BW sodium fluoride) and one osteosarcoma in the 100ppm male rats (5.2 mg/kg BW sodium fluoride).

When the NTP and the P&G studies are combined, there is a total of 8 individual sex/species groups examined. Seven of these groups showed no significant evidence of malignant tumor formation. One of these groups, male rats from the NTP study, showed “equivocal” evidence of carcinogenicity, which is defined by NTP as a marginal increase in neoplasms – i.e. osteosarcomas – that may be chemically related. Taken together, the two animal studies available at this time fail to establish an association between fluoride and cancer.

International Programme on Chemical Safety. (1984). Environmental health criteria 36: Fluorine and fluorides. Geneva, Switzerland: World Health Organization.

Page 85: Cancer mortality rates in areas with different amounts of fluoride naturally present in the drinking water have been compared in a considerable number of epidemiological studies. These studies have been carefully reviewed and evaluated by IARC (1982) with the following conclusions: “When proper account was taken of the differences among population units in demographic composition, and in some cases also in their degree of industrialization and other social factors, none of the studies provided any evidence that an increased level of fluoride in water was associated with an increase in cancer mortality.” Thus “variations geographically and in time in the fluoride content of water supplies provide no evidence of an association between fluoride ingestion and mortality from cancer in humans.”

Other Reviews

(examples of municipal or territorial reviews of the water fluoride issue)

Lepo, J.E. & R.A. Snyder (2000, May). (On-line). Impact of Fluoridation of the Municipal Drinking Water Supply: Review of the Literature. Prepared for the Escambia County Utilities Authority. The Center for Environmental Diagnostics and Bioremediation.

Page 15: There is no epidemiological evidence linking fluoride with increased rates of cancer. The International Agency for Research on Cancer (1982) compiled demographic data comparing cancer rates in regions with naturally or artificially fluoridated water to those in regions with low fluoride levels. The IARC found no correlation of cancer rates with fluoride exposure. Similar investigations performed by the EPA (USEPA, Fed Register, 1985b) and the National Research Council (1977) likewise found no correlation of fluoride levels with cancer.

The National Cancer Institute (NCI) evaluated the relationship between fluoridation and cancer mortality in the US during a 36-year period and a 15-year period. There were 2.2 million cancer death records and 125,000 cancer case records in counties using fluoridated water but there was no correlation between cancer cases and fluoridated drinking water. These statistics speak volumes: considering that the exposure to so many carcinogenic substances are so easily correlated with the epidemiology of cancer, and indeed exposure to non-carcinogenic substances can be correlated to cancer, it is remarkable that to date no epidemiological correlation of fluoride exposure to cancer incidence has been demonstrated.

Locker, David. (1999). Benefits and risks of water fluoridation. An update of the 1996 federal-provincial sub-committee report. Prepared under contract for the Public Health Branch, Ontario Ministry of Health, First Nations Inuit Health Branch, Health Canada. University of Toronto: Community of Dental Health Services Research Unit, Faculty of Dentistry.

Page 6, summary: The few studies published during the review period do not challenge earlier research showing there is no reason to believe that exposure to fluoridated water increases the risk of cancer in bones or other body tissues. While an ecological study did suggest an association with uterine cancer, the limitations of this kind of study in terms of linking exposures and outcomes in individuals, mean that it does not contradict the evidence derived from more systematic and scientifically credible case-control studies.

Page 52: Numerous studies have been undertaken to determine if water fluoridation is linked to increases in the risk of cancer. Many studies claiming that such a risk exists have been re-analyzed and found to provide no evidence of a link. Moreover, many used the correlational ecologic design, which has significant limitations in terms of establishing cause and effect relationships.

A recently published ecological study (Tohyama, 1996) did find a significant correlation between fluoride concentration in drinking water and uterine cancer mortality in 20 municipalities in Okinawa, Japan. This association remained

significant after adjusting for a number of confounders such as population ratio, income gap, still birth rate and divorce rate. However, the study did not control for more relevant confounders such as smoking and sexual activity.

A 1990 animal study showing a possible link between fluoride and osteosarcoma stimulated a number of more rigorous studies using case-control designs, which were published between 1994 and 1999. Three case-control studies from the US found no association between exposure to fluoridated drinking water and osteosarcoma (Moss et al., 1995; McGuire et al., 1995; Gelberg et al., 1995). For example, a multi-center study involving 147 patients and 248 controls found no differences between the proportions exposed to optimally fluoridated water or average yearly exposure (McGuire et al., 1995). The study by Gelberg et al. (1995) found no association between fluoride exposure and osteosarcoma in a study of 130 cases aged 24 years or less and 130 age and sex matched controls. The finding of no association held whether fluoride exposure was based on data provided by patients or their parents. The study also suggested that there might be a protective effect for males.

Studies of other cancer sites, one an ecologic study from South Africa (Borner & Aggett, 1994) and a case-control study of bladder, colon, and rectal cancer in Ontario (Marrett & King, 1995) showed no association between water fluoridation and increased risk of cancer. Two recent reviews of the literature also concluded that there is no evidence that fluoride in the water supply is linked with an elevated risk of cancer at any body site (Cook-Mozaffari, 1996; Cantor, 1997).

Report of the expert panel for water fluoridation review. (March 1998). City of Calgary, and Calgary Regional Health Authority: Appointed by the Standing Committee on Operations and Environment.

Summary majority opinion, page 30: From the perspective of epidemiology and toxicology, the available scientific literature has not substantiated the claims that water fluoridation was a factor in other adverse health effects. The results found in the literature have not eliminated the need for further research.

The Lord Mayor's taskforce on fluoridation – final report. (1997). Brisbane, Australia: Brisbane City Council.

Cancer (Pages 50-51): There were upwards of 50 published reports of studies looking at the association between water fluoridation and cancer. The majority of these studies reported no significant association between fluoride and cancer rates thus providing no evidence that fluoridation was a cause of cancer. One study from the US reported a statistically significant positive association in 1977. However, in this type of study it was impossible to rule out confounding as a possible explanation for any association seen. Furthermore, the study has been heavily criticized in the literature for the way in which the analysis was performed, and re-analyses of the same data have consistently shown no association.

Using the classification above, all of this evidence would be classed as level 1 or possibly level 2 and, in the absence of any stronger data there was, therefore, no scientific evidence on which to base an evaluation of causality. There have also been several studies looking at the specific association between fluoride and the risk of osteosarcoma. Again the majority of these were conducted at the population level and found no association between water fluoride levels and either osteosarcoma or bone cancer rates generally. Three further studies considered individuals with and without bone cancer, and could, therefore, be considered to provide stronger evidence for an evaluation of causality. Of these, the two largest and most recent studies found no consistent association between osteosarcoma and fluoride. The earliest study was very small and reported a significant protective effect associated with fluoride.

In summary, the majority of the data would be classed as level 1 and there was none of level 3 which would be required to provide any reliable evidence of causality. There was, therefore, no scientific evidence to support claims that water fluoridation causes osteosarcoma.

Natick Fluoridation Study Committee. (1997). Should Natick fluoridate?: A report to the town and Board of Selectmen. (On-line).

Page 4, finding: Animal bioassays suggest that fluoride is a carcinogen, especially for tissues such as bone (osteosarcoma) and liver. The potential for carcinogenicity is supported by fluoride's genotoxicity and pharmacokinetic properties. Human epidemiology studies to date have been inconclusive, but no appropriate major study has been conducted.

Page 36-37: The animal study conducted by the National Toxicology Program (NTP) provides evidence that fluoride causes osteosarcoma, a malignant bone tumor. Although the NTP concluded that its study gave "equivocal" results with respect to cancer, the background memos and documents suggest that the results are actually stronger

than suggested by the report. Similarly, the P & G study likely gave stronger evidence of carcinogenicity, notably bone cancer, than suggested in the summary statements.

That fluoride is associated with bone cancer is reasonable from the point of view of what is known about the effects of fluoride: fluoride causes the division of immature bone cells (proliferation of osteoblasts) and fluoride accumulates in the bone and thus can cause damage there. Fluorine has been shown to be genotoxic in numerous test systems, which is another property that is associated with carcinogens. In other words, the biochemistry, pharmacokinetics, and other toxicology studies support the view that fluoride may be a bone carcinogen.

Epidemiology studies examining cancer in general and bone cancer in particular have been inconsistent. Studies using ecologic designs (the studies are based on cancer incidence or mortality for given geographic areas, not for individuals) have given conflicting results for cancer in general, for all bone cancer, and for osteosarcoma. The larger case-control studies do not show an association of fluoride or water fluoridation with bone cancer although at least one small study has shown an association. Most of these studies are handicapped by completely inadequate measures of exposure, which would mask any effects that may be there because of non-differential misclassification of exposure. Given the widespread deliberate exposure of humans to water fluoridation and the suggestive animal data regarding cancer, especially osteosarcoma, it is incomprehensible why a large case-control epidemiology study with good measures of fluoride exposure has not been initiated.

Topic: BONE FRACTURES AND OTHER BONE EFFECTS

(not including bone cancer or skeletal fluorosis)

Major “Tier One” Reviews (United States, World Health Organization, & York)

Medical Research Council. Medical Research Council working group report: water fluoridation and health. (September 2002).

Pages 27-29: 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 fluoride concentration of 1ppm in water were 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.

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 1ppm 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 (i.e., worst case estimate) for the relative risk of hip fracture from a water fluoride concentration of 1ppm 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%, i.e., 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 US 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.

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.

Exposure issues. Many of the epidemiological studies on fluoride and bone health have only assessed risk in relations 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 high 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.

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.

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. 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.

Feasibility of research. A study to assess the bioavailability of fluoride 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 minimize 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 include 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.

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 difference 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 concern, are of lower priority.

Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. (2001 draft and 1993).
Toxicological profile for fluorides, hydrogen fluoride, and fluorine.

Pages 83-84: Numerous studies have examined the possible relationship between exposure to fluoride in drinking water and the risk of bone fractures. Many of these studies are ecological studies that examined communities with high level of fluoride in the water or fluoridated water (Arnala et al., 1984; Cooper et al., 1990, 1991; Danielson et al., 1992; Jacobsen et al., 1990; Kroger et al., 1994; Madans et al., 1983; Simonen & Laitinen, 1985; Sowers et al., 1986); a few prospective (Cauley et al., 1983; Simonen & Laitinen, 1985; Sowers et al., 1986); a few prospective (Cauley et al., 1995; Phipps et al., 2000) or retrospective (Kurtio et al., 1999) studies have also examined this

possible association. These studies have found conflicting results, with studies finding a higher or lower incidence of hip fractures or no differences in hip fracture between humans exposed to fluoride in drinking water. Several studies have found decreases in hip fracture incidences in communities with fluoride in the drinking water, suggesting that there may be a beneficial effect. Simonen and Laitinen (1985) examined male & female residents older than 50 years of age living in two cities in Finland with either trace amounts of fluoride in the water or with 1ppm fluoride in the water. The occurrence of femoral neck fractures was lower in men 50-80 years old and women >70 years old living in the area with fluoridated water, as compared to the low fluoride community. No difference in femoral neck fracture was observed in women 50-69 years of age. Madans et al. (1983) examined the association between fluoride in drinking water and risk of hip fractures using hip fracture data for the National Health Interview Surveys of 1973-77 and CDC data on the percent of a population in each US county served with water having natural or adjusted fluoride content of at least 0.7 ppm in 1963. Female residents over 45 years of age living in areas with lower fluoride levels in the drinking water had 9% more hip fractures than women living in high fluoride areas; however, the difference was not statistically significant. In a prospective study of older women, Phipps et al. (2000) examined the possible relationship between living in an area with fluoridated water and the risk of fractures. Higher bone mineral density of the lumbar spine and femoral neck and trochanter and lower bone mineral density of the radius were observed in women continuously living in an area with fluoridated water, as compared to residents in a non-fluoridated water area. Fewer spine, hip, and humerus fractures were also observed in this group. However, a higher incidence of wrist fractures was also observed in this group. Cauley et al. (1995) examined a subset of this population, and found no effect on age-adjusted axial and appendicular bone mineral density and no effect of the risk of vertebral or non-vertebral fractures.

Page 84: In contrast to the results of these studies, other studies have found an increase in the incidence of hip fractures in communities with fluoride in the drinking water. Sowers et al. (1986) examined female residents living in three communities in northwest Iowa with either high fluoride (4 mg/L)-low calcium (14-19 mg/L), low fluoride (1 mg/L)-high calcium (336-390 mg/L), or low fluoride (1 mg/L)-low calcium (62-71 mg/L) levels in the drinking water. The subjects had lived in the communities for at least 5 years and did not have wrist or forearm fractures in the previous 2 years. Among women 55-80 years old living in the high fluoride community, bone mass of the radius was significantly lower and a higher incidence of hip fractures was observed, as compared to the other groups. No effect was seen in younger women (20-35 years old). A geographical correlational study of 541,985 white women hospitalized for hip fractures found a weak association (regression coefficient = 0.001, $p=0.1$) between hip fracture incidence and fluoridation of water (Jacobsen et al., 1990). The association was strengthened (regression coefficient = 0.003, $p=0.0009$) after correcting by county for other factors found to correlate with hip fracture incidence (latitude, hours of sunlight, water hardness, income levels, and percentage of land in farms).

Page 85: A study in England and Wales also found increased rates of hip fractures in men and women over age 45 as water fluoride levels increased up to 0.93 ppm (Cooper et al., 1991). Hip fracture rates in 39 counties (standardized by age and sex) were compared with water fluoride levels in those counties. In the original analysis (Cooper et al., 1990), no significant correlation was found. However, when the authors reanalyzed the data using a weighted least-squares technique to account for the differences in the precision of the county specific rates, a significant positive correlation between water fluoride levels and hip fracture rates was found ($r=0.41$, $p=0.009$). The correlation existed for both women ($r=0.39$, $p=0.014$) and men ($r=0.42$, $p=0.0007$) (Cooper et al., 1991). Kurttio et al. (1999) studied over 144,000 residents living in rural areas of Finland from 1967-80. When all age groups were considered together, no relationship between fluoride levels in drinking water and the risk of hip fractures was found. However, among women aged 50-64 years with higher fluoride levels, an increase in the risk of hip fractures was found. No consistent relationships were found in men or older women. The study authors suggested that the other risk factors for hip fracture may be more important than fluoride exposure in determining the risk of hip fracture in older women. An ecologic cohort study compared the hip fracture rate for men and women in a Utah community that had water fluoridated to 1 ppm with the rate in two communities with water containing <0.3 ppm fluoride (Danielson et al, 1992). Fluoridation began in the fluoridated community in 1966. The age-adjusted rate was significantly elevated in both women (relative risk 1.27, 95% CI 1.08-1.46) and men (relative risk 1.41, 95% CI 1.00-1.81). In men, the rates in the fluoridated and nonfluoridated communities were similar until age 70. From age 75 on, the difference between the rates in the fluoridated and nonfluoridated areas increased with age. The difference between the hip fracture rates in the fluoridated and non-fluoridated areas increased for women in the 70 and 75-year age groups. However, the fracture rates in women at ages ≥ 80 years old were similar in the fluoridated and non-fluoridated towns. The study authors attributed this to the fact that women older than 80 years of age would have already gone through menopause by the beginning of fluoridation, and so would have had less bone remodeling and less incorporation of fluoride into the bone. The study authors also suggested that the reason that they found an effect when other investigators have not was the low levels of exposure to risk factors for osteoporosis (smoking and

alcohol) in the Utah populations. This was a well-conducted study that suggests that communities with fluoridated water have an elevated risk of hip fracture. However, several possible confounding factors were not examined. Calcium levels in the water, total calcium and vitamin D intake, and individual fluoride intake were not determined. Estrogen use was not evaluated, but was assumed to be similar since the communities were similar distances from larger medical centers. In addition, estrogen levels would not cause the effect in men.

Pages 85-86: Other studies have not found a relationship between fluoride in drinking water and hip fracture prevalence. No significant differences in the incidence or type of upper femoral fracture were observed when groups of subjects living in communities with low fluoride (0.3 ppm), fluoridated (1.0-1.2 ppm), or high fluoride (>1.5 ppm) drinking water (Arnala et al., 1986). An increase in the fluoride content of bone and an increase in the volumetric density of the osteod were observed in the residents in the high fluoride area. Kroger et al. (1994) found no effect on self-reported fractures among a group of older Finnish residents (mean age approximately 53 years) living in an area with fluoridated water (1.0-1.2 mg/L), as compared to residents living in an area with low fluoride levels in the drinking water (<0.3 ppm). Increases in spine and femoral neck bone mineral density were observed in the fluoridated water group.

Page 87: Haguenaer et al. (2000) performed a meta-analysis to examine the effects of fluoride on the treatment and prevention of post-menopausal osteoporosis using the data from Riggs et al. (1990, 1994), Kleerekoper et al. (1991) and 10 other studies. The meta-analysis showed a significant increase in bone mineral density in the lumbar spine and hip and a decrease in bone mineral density in the forearm after 2 or 4 years of fluoride treatment. When the data from all the studies was used, fluoride treatment for 2 or 4 years did not affect the relative risk of vertebral fractures. However, in studies in which the subjects were exposed to low levels of fluoride or a slow-release formulation for 4 years, a significant decrease in vertebral fracture risk was seen. An increase in the relative risk of non-vertebral fracture was observed when the data from all sources were used; no effect was seen in studies using low levels of fluoride (<30 mg/day) or slow-release fluoride.

Results of animal studies are included on page 87-88 (not included here)

NHS Centre for Reviews and Dissemination, University of York. (2000). [A systematic review of public water fluoridation](#). York, UK: York Publishing Services Ltd.

Discussion page 53. There were 29 studies included on bone fracture and bone development problems. Other than fluorosis, bone effects (not including cancers) were the most studied potential adverse effect. These bone studies also had a low validity (3.4 out of 8) with all but one study being evidence level C. These studies included both retrospective and prospective cohort designs, some of which included appropriate analyses controlling for potential confounding factors. Observer bias could potentially play a role in bone fracture, depending on how the study is conducted.

The graph of estimates of association for all bone fracture studies shows that the individual estimates of effect lie very close to a relative risk of 1.0. Most of the confidence intervals cross 1.0 (statistically non-significant). The only confidence intervals that do not include 1.0 (statistically significant) are evenly distributed, five indicating an increased risk of fracture and four indicating a decreased risk. The meta-regression showed that the pooled estimate of the association of bone fracture with water fluoridation was 1.00 (0.94, 1.06), however due to the significant heterogeneity between the studies this value should be interpreted with extreme caution. The meta-regression showed that the only variable (out of 30 total) associated with the summary measure at the 5% significance level was duration. Factors, which would be expected to show an association with fracture incidence, such as fracture site, age, and sex, were not associated with water fluoride level at the 5% significance level in either the univariate or multivariate models. This adds support to the result suggested by the pooled estimate of no association between water fluoridation and fracture incidence.

The evidence on bone fracture can be classified into hip fracture and other sites as there were a greater number of studies on hip fracture than any other site. Using a qualitative method of analysis, there is no clear association of hip fracture with water fluoridation. Of 18 studies, three showed a statistically significant benefit, and two showed statistically significant harm, and three showed no effect of water fluoridation on hip fracture. One study found no cases of hip fracture in the low fluoride group, indicating harm from water fluoridation. The evidence on other fractures is similar; of 30 study comparisons one found statistically significant benefit, one found statistically significant harm and three found no effect. The evidence on other bone outcomes was extremely limited. A negative association was suggested in the risk of slipped epiphysis in boys, but this finding was not statistically significant.

Committee on the Scientific Evaluation of Dietary Reference Intakes. (1999). Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, D.C.: National Academy Press.

Page 300: Several reports published 30 to 40 years ago suggested that the long-term ingestion of fluoride at levels slightly above optimum for caries prevention improved the quality of the human skeleton (Bernstein et al., 1966; Leone et al., 1955, 1960). A recent Finnish study concluded that, compared with the low-fluoride control group, vertebral bone mineral density (BMD) was increased slightly while femoral neck BMD was not affected among peri-menopausal women who had used fluoridated water (1.0 to 1.2 mg/liter) for 10 years or more (Kroger, 1994). There was no difference between the groups in the prevalence of self-reported bone fractures. Richards et al. (1994) reported that the normal, age-related increase in bone fluoride concentrations (range 463-4,000 mg/kg) had no effect on the compressive strength or ash density of vertebra in Danish men and women whose ages ranged from 20 to 91 years. Sowers et al. (1986, 1991), however, reported a marginal increase in bone fractures (self-reported) and lower bone densities among women whose drinking water contained 4 mg/liter of fluoride.

World Health Organization. (1994). WHO technical report series #846: Report of a WHO expert committee on oral health status and fluoride use. Geneva, Switzerland: World Health Organization.

Page 11: Several recent epidemiological studies of long-term exposure to fluoride in drinking water at optimal levels for caries prevention have reached conclusions implicating fluoride as the causative factor in the increasing incidence of hip fractures in the elderly, owing to increased brittleness of the cortical bone plates. However, independent reviews of these contemporary studies conclude that they fail to establish an adequate basis for concluding that fluoride levels in drinking water are related to hip fractures and bone health (Gordon et al., 1992). Most of the studies have important limitations that restrict generalization of their results either to the population as a whole or to determining risks for individuals. Therefore no basis exists for altering current public health policy on the use of fluorides for caries prevention.

National Research Council. (1993). Health effects of ingested fluoride. Washington, D.C.: National Academy Press.

Pages 6-7: The effect of fluoride on bone strength, hip fractures, and skeletal fluorosis in humans has been addressed in 2 types of studies. The first type involves clinical trials of the effectiveness of high concentrations of fluoride supplements in strengthening bones and preventing further fractures in patients with osteoporosis; this treatment has been used primarily in Europe for almost 30 years. When conducted using proper control groups, these studies showed little or no benefit even at dosage of 20-32 mg per day, well over 10 times the exposure from fluoridated drinking water. If anything, the treated groups experienced a greater number of new fractures, including painful stress fractures in bones other than the vertebrae.

The second type of human study involves epidemiological investigations. These studies compared the rate of bone fracture in populations of the elderly that differed in their exposure to natural or added fluoride in drinking water. Geographic and time-trend analyses were made; time-trend analysis is considered the stronger methodology because there is less opportunity for confounding by other risk factors. Of the 6 epidemiological studies that used geographic comparisons (where no actual intake data were available), 4 found a weak association between fluoride in drinking water and risk of hip fracture. Two additional studies examined time trends in bone fracture before and after water fluoridation: one found no association and the other a negative association. Only two additional studies collected information on individual exposure: one (essentially a geographic comparison) found an increased risk of hip fracture at water fluoride concentrations of 4 mg/L, and the other observed no differences in risk.

Studies with several species of experimental animals have yielded various outcomes. Most of the studies indicated little or no negative effect on bone strength, even with very high fluoride intake and very high concentrations of fluoride in bone. The subcommittee identified many potential problems in the experimental design of the animal studies, including the lack of suitable control groups with reasonably low fluoride exposures. However, the subcommittee concluded that the weight of evidence indicates that bone strength is not adversely affected in animals that are fed a nutritionally adequate diet unless there is long-term ingestion of fluoride at concentrations of at least 50 mg/L of drinking water or 50 mg/kg in diet.

In view of the conflicting results and limitations of the current database of fluoride and the risk of hip fractures, the subcommittee concludes that there is no basis at this time to recommend that EPA lower the current standard for fluoride in drinking water for this end point.

Committee to Coordinate Environmental Health and Related Programs, USPHS. (1991). Review of fluoride: Benefits and risks: Report of the subcommittee on fluoride of the EHPC. Public Health Service: Department of Health and Human Services.

Page 5 of executive summary: Although some epidemiologic studies have suggested that the incidence of certain types of bone fractures may be higher in some communities with either naturally high or adjusted fluoride levels, other studies have not detected increased incidence of bone fractures. However, a variety of potentially confounding factors must be examined to assess whether there is an association between exposure to fluoride and bone fractures.

Osteogenic Effects and Bone fractures, page 48: The issue of the role of fluoride in the etiology of bone fractures initially appeared as a consequence of the findings of clinical trials using fluoride as a treatment for osteoporosis. However, several community studies have further investigated this relationship. In one study, 39 countries with varying levels of calcium and concentrations of fluoride ranging from 0.005 mg/L in Sandwell to 0.93 mg/L in Birmingham, UK were compared. No significant correlations were found between the level of water fluoridation or calcium and the prevalence of hip fractures. (Cooper, 1990).

Another geographical correlational study of hip fracture in the US observed a small but positive correlation between the incidence of hip fracture and diet, calcium content, and fluoride levels (Jacobsen et al., 1990). In the most comprehensive study to date, Sowers and coworkers (in press) studied women in three demographically similar rural communities. The communities were identified on the basis of both fluoride and calcium levels in the drinking water supplies. One community (high fluoride, low calcium) had natural levels of fluoride of 4 mg/L and calcium levels of 15 mg/L; the second community had fluoride levels of 1 mg/L and calcium levels of 67 mg/L. There were no significant differences in the five-year risk of fractures occurring at the wrist, spine, or hip in the high calcium versus the control community, there was a two-fold increased risk of fractures of all sites in among women 55-80 years of age in the higher fluoride community when compared with the control community. Possible confounding factors such as hormone use, body size and weight, age, and dietary intake of calcium were examined and were not found to be exerting any differential effects in the study communities.

Currently, the body of data on the role of fluoride in the etiology of fractures is not resolved.

Page 87: There is some suggestion from epidemiological studies that the incidence of certain bone fractures may be greater in some communities with either naturally high or adjusted fluoride levels. However, there are a number of confounding factors that need resolution to determine whether or not an association exists. Additionally, other studies do not show an increase in the incidence of bone fractures; one study provided evidence of a lower incidence of bone fractures in an optimally fluoridated community as compared to a similar community with trace levels of fluoride in the water. Therefore, further research is required.

Other Reviews

(examples of municipal or territorial reviews of the water fluoride issue)

Lepo, J.E. & R.A. Snyder (2000, May). (On-line). Impact of Fluoridation of the Municipal Drinking Water Supply: Review of the Literature. Prepared for the Escambia County Utilities Authority. The Center for Environmental Diagnostics and Bioremediation.

Page 14: In clinical trials, high doses of sodium fluoride such as 75 mg/day produced bone that was less mechanically strong than regular bone, but a lower dose (25 mg/twice daily with a slow release of F) produced fewer new vertebrate fractures and higher bone mass with minimal effects (Cerklewski, 1997). Fluoride's role in bone development is well documented (Cerklewski, 1997), and a report that lifetime of fluoride exposure was associated with increased hip fracture has not been supported by others.

Locker, David. (1999). Benefits and risks of water fluoridation. An update of the 1996 federal-provincial sub-committee report. Prepared under contract for the Public Health Branch, Ontario Ministry of Health, First Nations Inuit Health Branch, Health Canada. University of Toronto: Community of Dental Health Services Research Unit, Faculty of Dentistry.

Page 5, summary: Studies of the association between water fluoridation and bone fracture are largely ecological in design. Of 11 studies published prior to 1994, two showed a protective effect, five showed no association and four suggested an increase in hip fracture rates. In the latter, the strength of the association was weak, with relative risks

ranging from 1.1 to 1.4. Of four studies published between 1994 and 1999, one showed a non-significant protective effect, two showed no association and one suggested an increased risk (RR= 1.3-1.4). The public health significance of small increases in hip fracture rates in elderly populations means that more studies with better research designs are needed.

Pages 45-51: The conclusions reached by each of these studies are limited since they used an ecologic measure of fluoride exposure. The associations found in studies using aggregate level data may differ from the associations measured with individual level data are collected [sic]. Even when the residential history is determined for each subject, the measurement of the fluoride exposure may be biased since the fluoridation of the public water supplies does not necessary mean that all residents are equally exposed and individual variations in water intake can be such that residents of different communities have similar fluoride intakes. In addition, ecological studies do not allow for the control of potential confounders and effect modifiers. In the studies with a hybrid design this has been overcome to some degree by collecting data on variables known to be cofounders [sic] on the individual level. Therefore, the association observed in an ecological study is always tenuous. Nevertheless, consistency of evidence across studies should enhance the overall credibility of risks or benefits suggested by ecological data. Since the results of the ecological studies on water fluoridation and hip fracture have been far from consistent, the possibility of a cause-effect relationship cannot be established. Consequently, the studies conducted to date do not provide systematic and compelling evidence of an adverse effect on bone.

Report of the expert panel for water fluoridation review. (March 1998). City of Calgary, and Calgary Regional Health Authority: Appointed by the Standing Committee on Operations and Environment.

Summary majority opinion, page 30: The scientific literature on fluoride and bone fractures, especially hip fractures in the elderly, did not provide evidence that would lead to substantial changes in water fluoridation policy. Questions about exercise and activity, calcium and vitamin D intake, overall health status, other sources of fluoride, use of other medication, and general standards of osteoporosis medical practice in the studied communities have to be addressed before the results of the inconclusive epidemiological studies can be confirmed.

The Lord Mayor's taskforce on fluoridation – final report. (1997). Brisbane, Australia: Brisbane City Council.

Osteoporosis and Hip Fracture (Page 50): A series of studies, mostly conducted in the USA, the UK and Canada, have addressed the question of whether fluoride affects the risk of fracture of the hip. In summary, of 17 ecological studies (i.e. studies of groups or populations), six reported no association with hip fracture, two a significant decrease in risk and nine and increased risk of fracture, although this was not statistically significant in three studies.

None of the studies provided strong evidence of an association, at the levels of fluoride used for artificial fluoridation, that cannot be explained by chance, bias or confounding. In summary, there was no evidence that could be classed as level 3 and used reliably to evaluate causality.

Natick Fluoridation Study Committee. (1997). Should Natick fluoridate?: A report to the town and Board of Selectmen. (On-line).

Page 3, findings: Water fluoridation shows a positive correlation with increased hip fracture rates in persons 65 years of age and older, based on two recent epidemiology studies.

Page 34: In a national study of ecological design Jacobsen et al. (1992) examined the association between water fluoridation and the incidence of hip fractures. For the period 1984-87, a total of 218,951 eligible hip fracture cases were studied. Raheb (1995) characterized the results of Jacobsen's study as "a small, statistically significant positive association was found between fluoridation and fracture incidence rates." However, a careful review of the data of Jacobsen and his coworkers show an 8% increase in women (+/- 2%) and a 17% increase for men (+/- 4%). A more recent study on a smaller population (which was restricted to Mormon communities in Utah to correct for confounding factors such as smoking and or use of alcohol) showed an increased incidence of hip fractures of 27% in women and 41% in men, albeit with a larger 95% confidence interval (Danielson, 1992). While four other studies indicate either no effect or a negative effect of fluoridation, these studies involved a total of only 6,874 subjects as opposed to positive correlation in the case of 781,575 subjects.

Page 34, summary: Well-controlled studies have not demonstrated a beneficial effect of the use of high doses of fluoride in reducing osteoporosis and related bone fractures. However, there has been a positive relationship between water fluoridation and increase hip fractures in persons 65 years of age and older.

Topic: SKELETAL FLUOROSIS

Major “Tier One” Reviews (United States, World Health Organization, & York)

Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. (2001 draft and 1993). Toxicological profile for fluorides, hydrogen fluoride, and fluorine.

Pages 81-83: Fluoride results in thickened bones and extoses (skeletal fluorosis) when ingested in large doses for an extended period of time. Reported cases are found almost exclusively in developing countries, particularly India, and are associated with malnutrition (Pandit et al., 1940). Tea consumption and high water intake due to tropical climate are probably also contributing factors. It is generally stated that a dose of 20-80 mg/day (equivalent to 10 to 40 ppm in the water) is necessary for the development of crippling skeletal fluorosis (NAS, 1971a), but individual variation, variation in nutritional status, and the difficulty of determining water fluoride levels in such situations make it difficult to determine the critical dose. Pandit et al. (1940) found severe skeletal fluorosis in people who had consumed 13-24 mg/day for >15 years.

The incidence of skeletal fluorosis in the US is unknown, since it appears that the early signs can only be identified radiologically. A study of 116 people who had lived in an area with an average of 8ppm fluoride in the drinking water for at least 15 years found a 10-15% incidence of fluoride-related bone changes (Leone et al., 1955). Coarsened trabeculation and thickened bones were observed, but no extoses were evident, and the subjects were asymptomatic.

A limited number of cases of crippling skeletal fluorosis due to oral exposure have been reported in the United States. Where the doses are known, they are generally in the 15-20 mg/fluoride/day for over 20 years; two of the cases were associated with renal disease, which would reduce fluoride excretion. Two of the cases were associated with drinking large quantities of water with >3.5 ppm fluoride.

Fluoride is found in all bone, with the concentration depending on total fluoride exposure. The amount varies among different bones. Levels of fluoride in human bone are generally determined by biopsy of the iliac crest bone, and are generally reported as ppm bone ash. Average bone contains 500-1,000 ppm fluoride. (Boivin, 1988; Franke, 1975). Bone from people with pre-clinical skeletal fluorosis, which is asymptomatic and characterized by slight radiologically detectable increases in bone mass, contains 3,500-5,500 ppm fluoride. Sporadic pain, joint stiffness, and osteosclerosis of the pelvis are observed at 6,000-7,000ppm, while chronic joint pain, increased osteosclerosis, and slight calcification of ligaments occur at 7,500-9,000ppm. Crippling fluorosis is observed at fluoride bone concentrations >10,000 ppm (Franke, 1975). The fluoride concentrations in bone increases with age (Zipkin, 1958). In a group of five people ages 64-85 that had lived for at least 10 years in an area with water containing 1 ppm fluoride, the average fluoride concentration of the iliac crest bone was 2,250 ppm of bone ash.

Committee on the Scientific Evaluation of Dietary Reference Intakes. (1999). Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, D.C.: National Academy Press.

Pages 307-308: Three recent reviews of the literature attempted to identify adverse functional effects of fluoride ingestion in adults (Kaminisky et al., 1990; NRC, 1993; USPHS, 1991). Fluoride exposures included those associated with drinking water containing as much as 8 mg/liter of fluoride and the use of dental products. These reviews indicate that the primary functional adverse effect associated with excess fluoride intake is skeletal fluorosis.

In the asymptomatic, pre-clinical stage of skeletal fluorosis, patients have slight increases in bone mass that are detectable radiographically, bone ash fluoride concentrations that range from 3,500 to 5,500 mg/kg, and bone concentrations that are 2 to 5 times higher than those of life-long residents of optimally fluoridated communities (Eble et al., 1992). Stage 1 skeletal fluorosis is characterized by occasional stiffness or pain in joints and some osteosclerosis of the pelvis and vertebra. Bone ash fluoride concentrations usually range from 6,000 to 7,000 mg/kg. In stages 2 and 3, bone ash concentrations exceed 7,500 to 8,000 mg/kg (Hodge and Smith, 1977). The clinical signs in stages 2 and 3, which may be crippling, may include dose-related calcification of ligaments, osteosclerosis, extoses, possibly osteoporosis of long bones, muscle wasting, and neurological defects due to hypercalcification of vertebra (Krishnamachari, 1986).

The development of skeletal fluorosis and its severity is directly related to the level and duration of exposure. Most epidemiological research has indicated that an intake of at least 10 mg/day for 10 or more years is needed to produce clinical signs of the milder forms of the condition. Hodge (1979) reported that evidence of crippling fluorosis “was not seen in communities in the United States where water supplies contained up to 20 ppm.” In such communities

daily fluoride intakes of 20 mg would not be uncommon. In a recent case report, severe joint pain and stiffness in a 64-year-old man were attributed to a fluoride intake of approximately 50 mg/day for 6 years. The well water ingested had a fluoride concentration of 25 mg/liter and a low calcium concentration (Boyle and Chagnon, 1995). Stevenson and Watson (1957) surveyed 170,000 radiographs of patients from Texas and Oklahoma whose drinking water fluoride concentrations ranged from 4 to 8 mg./liter. They identified 23 cases of osteosclerosis but no evidence of skeletal fluorosis.

Crippling skeletal fluorosis continues to be extremely rare in the United States (only 5 cases have been confirmed during the last 35 years), even though for many generations there have been communities with drinking water fluoride concentrations in excess of those that have resulted in the condition in other countries (Singh & Jolly, 1970). This puzzling geographic distribution has usually been attributed to unidentified metabolic or dietary factors that rendered the skeleton more or less susceptible.

Identification of a NOAEL and Critical Endpoint (Page 310): Epidemiological studies reported no detectable radiographic changes in bone density in persons in the United States exposed to drinking water containing less than 4 mg/liter of fluoride (McCauley & McClure, 1954; Schlesinger et al., 1956; Sowers et al., 1986; Stevenson & Watson, 1957). Leone (1955) compared bone x-rays of long-term residents of Bartlett & Cameron, Texas, which had water supplies with fluoride concentrations of 8.0 and 0.4 mg/liter, respectively. In this study, osteosclerosis was detected radiographically in 10-15% of individuals exposed to water containing 8.0 mg/liter of fluoride for an average of 37 years. However, no clinical symptoms of skeletal fluorosis were reported. Another report dealing with a variety of other medical conditions among residents of Bartlett and Cameron revealed no significant differences except for a slightly higher rate of cardiovascular abnormalities in Cameron residents (Leone et al., 1954). Therefore, based on the available data addressing the association between fluoride intake and skeletal fluorosis in North America, a NOAEL of 10 mg/day of fluoride was identified. This level of intake for some individuals would occur in areas where the drinking water has a fluoride concentration of 5 mg/liter and the diet is the main source of fluoride.

Uncertainty Assessment. Based on the fact that the NOAEL derives from human studies and the lack of evidence for symptomatic skeletal fluorosis observed at this level of fluoride intake, a UF of 1 was selected.

Derivation of the UL (Pages 310-311): The risk of developing early signs of skeletal fluorosis is associated with a fluoride intake greater than 10 mg/day for 10 or more years. Therefore a UL of 10 mg/day was established for children older than 8 years and for adults. Data from studies of fluoride exposure from dietary sources or work environments (Hodge & Smith, 1977) indicate the a UL of 10 mg/day for 10 or more years carries only a small risk for an individual to develop pre-clinical or stage 1 skeletal fluorosis.

Special considerations Page 311): Reports of relatively marked osteofluorotic signs and symptoms have been associated with concentrations of fluoride in drinking water of approximately 3 mg/liter in tropical climates. This adverse effect has been attributed to poor nutrition, hard manual labor, and high levels of water intake (Krishnamachari, 1986; Singh and Jolly, 1970; WHO, 1984). Therefore, an increased risk of skeletal fluorosis from excess fluoride intake may exist for malnourished individuals living in hot climates or tropical areas.

World Health Organization. (1994). WHO technical report series #846: Report of a WHO expert committee on oral health status and fluoride use. Geneva, Switzerland: World Health Organization.

Pages 7-12: Endemic, crippling skeletal fluorosis in temperate climates is confined to individuals exposed continuously over many years to very high levels of fluoride. These cases are associated with industrial situations or with unusually high fluoride levels in drinking-water (e.g. 10 mg/L). Fluoride-induced calcification of some tissues and osteosclerosis of bone are outcomes of long-term ingestion of unusually high levels of fluoride. Water fluoride levels of 4-8 mg/L in temperate climates have not been found to be associated with any clinical signs or symptoms of skeletal fluorosis. The situation, however, is different in some tropical areas; in a number of developing countries there have been reports that endemic skeletal fluorosis occurs in individuals whose drinking water contains more than 6 mg/L of fluoride. The condition manifests as osteosclerosis, osteoporosis, or an increase in woven bone. Crippling skeletal effects are observed in severe forms of fluorosis.

National Research Council. (1993). Health effects of ingested fluoride. Washington, D.C.: National Academy Press.

Pages 59-60: Smith and Hodge (1979) have described the pre-clinical and clinical stages of skeletal fluorosis. The asymptomatic pre-clinical stage is characterized by slight increases in bone mass that are detectable radiographically

and bone-ash fluoride concentrations between 3,500 and 5,500 ppm. The typical fluoride concentrations in bone ash from persons who have chronically consumed optimally fluoridated water are less than 1,500 ppm. In stage 1 of skeletal fluorosis, there might be occasional stiffness or pain in the joints and some osteosclerosis of the pelvis and vertebral column. Bone-ash fluoride concentrations in stage 1 usually range from 6,000-7,000 ppm. When bone-ash fluoride concentrations are 7,500-8,000 ppm or more, stages 2 and 3 of skeletal fluorosis are likely to occur. The clinical signs of these stages are chronic joint pain, dose-related calcification of ligaments, osteosclerosis, possibly osteoporosis of long bones, and in severe cases, muscle wasting and neurological defects.

Crippling skeletal fluorosis might occur in people who have ingested 10-20 mg of fluoride per day for 10-20 years. During the last 30 years, only five cases have been reported in the United States. The history of fluoride intake for two of the cases was determined with reasonable accuracy (Sauerbrunn et al., 1965; Goldman et al., 1971). The individuals consumed up to 6 L of water per day containing fluoride at 2.4-3.5 mg/L in one case and 4.0-7.8 mg/L in the other. The daily fluoride intake was estimated at 15-20 mg for 20 years. In general, this intake would be associated with a drinking-water supply containing fluoride at about 10 mg/L

Thus crippling skeletal fluorosis in the United States has been rare and not a public health problem (Leone et al., 1954; Stevenson & Watson, 1957), even though for many generations there have been communities with drinking water fluoride concentrations in excess of those that have resulted in the condition in other countries (Singh & Jolly, 1970). The puzzling geographic distribution of the disorder usually is ascribed to unidentified dietary factors that render the skeleton more or less susceptible.

The small number of cases of skeletal fluorosis in the United States has ruled out the possibility of systematic epidemiological evaluation. Based on limited data in the literature on skeletal fluorosis, the subcommittee concludes that skeletal fluorosis is not a public health issue in the United States.

Committee to Coordinate Environmental Health and Related Programs, USPHS. (1991). Review of fluoride: Benefits and risks: Report of the subcommittee on fluoride of the EHPC. Public Health Service: Department of Health and Human Services.

Page 5, executive summary: Fluoride has a complex dose-related action on bone. Although crippling skeletal fluorosis is more common in parts of the world with high natural fluoride (>10 ppm) levels in drinking water, its occurrence is affected by a variety of factors, including nutritional deficiencies, impaired renal function, and age at exposure. Human crippling skeletal fluorosis is endemic in several countries of the world, but is extremely rare in the United States.

Pages 45-47: The preclinical & three clinical stages of skeletal fluorosis (Smith & Hodge) are described in table 23, along with reported correlations of accumulated fluoride in bone ash to the osteosclerotic phase (Franke et al; Schlegel 1974). The earliest bone changes associated with skeletal fluorosis are radiographic enlargements of the trabeculae in the lumbar spine. These preclinical findings have been associated with bone ash fluoride concentrations of 3,500 to 4,500 ppm. Singh & Jolly (1970) reported that osteosclerosis in the pelvis and vertebral column, coarse trabeculae, and diffuse increased bone density of clinical phase I are seen in industrial cases but rarely are reported in areas where fluorosis is endemic. Most of the latter cases show the more severe changes of phases II or the crippling fluorosis of phase III. Bone changes observed in human skeletal fluorosis are structural and functional, with a combination of: 1) osteosclerosis, the predominant lesion in fluorosis patients who have an adequate dietary intake of calcium; 2) osteomalacia, which predominates in patients who have marginal or sub-optimal dietary intake of calcium; 3) osteoporosis and exostosis formation of varying degrees; and 4) secondary hypoparathyroidism in a proportion of patients (Krishnamachari, 1986).

Boivin and coworkers (1988) reported measuring bone fluoride content from iliac crest bone to determine the degree of fluoride retained in bone and, over time, the amount of fluoride eliminated. Subjects with skeletal fluorosis primarily of industrial etiology, had bone fluoride values over 0.50 percent of bone ash by weight, and the values were always statistically higher than the highest control value, 0.10% ($p < 0.001$). Fluoride retention in bone appeared to be higher in cases of greater fluoride exposure, even if that exposure was difficult to define precisely.

The total quantity of fluoride ingested is the single most important factor in determining the clinical course of skeletal fluorosis (Krishnamachari, 1986); the severity of symptoms correlates directly with the level and duration of exposure (Fisher et al., 1989). As most commonly reported for a person to develop crippling skeletal fluorosis, he or she must ingest 20 to 80 mg/day of fluoride (the equivalent to 10 ppm fluoridated water for 10 to 20 years (Hodge & Smith, 1965; Hodge, 1979; WHO, 1984; National Academy of Science (1980). For endemic, tropical areas, the level of clinical effect for skeletal fluorosis is less certain (NAS, 1980); Singh & Jolly (1970) stated that it may not be

possible to determine the average minimal dose of fluoride needed to produce skeletal fluorosis, because of individual variations and the crude level of water analysis in many of the endemic areas.

For almost 40 years, investigators in the US have searched for evidence of skeletal fluorosis. Radiographic changes in bone indicative of skeletal fluorosis, changes in bone mass, and effects on skeletal maturation were not observed at water fluoride concentrations of 1.2 mg/L for 10 years and from 3.3 – 6.2 mg/L for a lifetime (Hodge & Smith, 1981; Sowers et al., 1986; Schlesinger et al., 1956; McCauley & McClure, 1954). In a survey of 170,000 radiographs of patients living in Texas and Oklahoma with water fluoride levels between 4 - 8 mg/L, Stevenson & Watson (1957) found 23 cases of radiographic osteosclerosis, but no evidence of skeletal fluorosis.

Skeletal fluorosis is highly variable in its clinical severity among individuals living in the same environment and exposed to the same risk of fluoride ingestions (Krishnamachari, 1986). In the past 30 years, only five cases of crippling skeletal fluorosis have been reported in the literature in the US (Sauerbrunn et al., 1965; Goldman et al., 1971; Fisher et al., 1981 & 1989; Bruns & Tytle, 1988). Yet, over several generations many individuals in the US have consumed water containing high natural levels of fluoride, without demonstrating signs or symptoms of skeletal fluorosis. The unequal worldwide distribution of this disorder generally has been ascribed to unidentified dietary factors that render the skeleton more or less susceptible. Whitford (1989) suggests that differences among populations with respect to fluoride metabolism and fluoride balance are responsible. Acid-base status and the concomitant changes in urinary pH (Whitford & Reynolds, 1979) are the most important contributors to population variation.

In the 5 cases of crippling skeletal fluorosis in the US, retrospectively assessed, exposure to natural levels of fluoride in drinking water ranged from 3.9-8.0 mg/L. All possible confounding factors were not addressed. Two of these cases were associated with daily consumption of up to 6 liters of water containing fluoride levels of 2.4-3.5 ppm in one case and 4.0-7.8 ppm in the other (Sauerbrunn et al., 1965; Goldman et al., 1971). Large quantities of tea, itself high in fluoride, were consumed daily as well. The total fluoride intake was estimated to be 15-20 mg/day for 20 years.

Severe crippling fluorosis is not seen in all residents of endemic areas; age of exposure as well as dose and duration of fluoride intake are critical in predicting the clinical signs and symptoms of skeletal fluorosis. Other factors reported to influence the incidence of skeletal fluorosis include: nutritional and calcium deficiencies; renal insufficiency (Singh & Jolly, 1970); the level of bone turnover (Boivin et al., 1988); and diets containing high levels of fluoride (Sauerbrunn et al., 1965; Goldman et al., 1971). Also, in certain occupational settings, the duration and exposure from the inhalation of products of manufacturing, e.g. aluminum, steel, iron, pesticides, fertilizers, and smelting of precious metals (Hodge & Smith, 1972). Other factors influencing skeletal fluorosis include soil type or areas of volcanic rock, geophasia, syndromes of polydipsia, excessive water consumption (Fisher et al., 1989), and the type of physical activity (Singh & Jolly 1970). Finally, the following factors have been associated with increased incidence of skeletal fluorosis: pre-existing inflammation; increased serum haptoglobin levels; cortisol levels (Susheela et al., 1988); the use of fluoride in the treatment of inflammatory conditions (Bruns & Tytles, 1988).

International Programme on Chemical Safety. (1984). Environmental health criteria 36: Fluorine and fluorides. Geneva, Switzerland: World Health Organization.

Pages 77-78: On the basis of an extensive epidemiological survey, Singh & Jolly (1970) stated that crippling fluorosis was the result of continuous daily intake of 20-80 mg fluoride for 10-20 years. On the basis of more recent balance studies on patients with endemic fluorosis, which showed an average daily fluoride intake of 9.88 mg, Jolly (1976) suggested that a daily intake exceeding 8 mg in adults would be harmful. In tropical areas with endemic fluorosis, high fluoride levels in the drinking water seem to constitute an important factor in a multi-factorial causation (Reddy, 1979). Thus, poor nutrition, including calcium deficiency, and hard manual labor seem to play an additional role. In addition, protein deficiency may increase individual susceptibility to fluorosis (Siddiqui, 1955; Singh et al., 1961a).

In non-tropical countries, no cases of skeletal fluorosis with clinical signs and symptoms have been detected in relation to drinking water containing fluoride levels of less than 4 mg/liter (Victoria Committee, 1980). In Bartlett, Texas, with a (previous) water-fluoride level of 8-mg/ liter, radiological evidence of fluorosis in the form of osteosclerosis was recorded in 10-15% of the people (Leone et al., 1955). X-ray changes were also noted in a few people living in Oklahoma and Texas where the drinking water contained a fluoride level of 4-8 mg/liter (Stevenson & Watson, 1957). In other studies, no signs or symptoms of osteofluorosis were detected in areas with fluoride levels of up to 6 mg/liter in water supplies (McClure, 1946; Eley et al., 1957; Knishikov, 1958).

Other Reviews

(examples of municipal or territorial reviews of the water fluoride issue)

Locker, David. (1999). Benefits and risks of water fluoridation. An update of the 1996 federal-provincial sub-committee report. Prepared under contract for the Public Health Branch, Ontario Ministry of Health, First Nations Inuit Health Branch, Health Canada. University of Toronto: Community of Dental Health Services Research Unit, Faculty of Dentistry.

Pages 44-45: The intake of fluoride at high levels for protracted periods results in a systemic osteosclerosis known as skeletal fluorosis or osteofluorosis. This condition is characterized by 1: a thickened cortical and cancellous bone with signs of hypomineralization and mineralization defects; 2. spur bony formations at tendon insertions; and 3. ossification of interosseous membranes and ligaments. These changes are more pronounced in the central skeleton and to a lesser degree in the skull and the peripheral bones (Fejerskov, 1996). Clinically they range from asymptomatic radiographic bone mass increase to crippling skeletal fluorosis involving spine and joint deformities and dysfunctions, muscle wasting and neurological problems due to spinal cord compression (Whitford, 1996; Kleerekoper, 1996).

Most estimates indicate that crippling fluorosis is associated with chronic fluoride exposures of ≥ 10 mg/day for at least 10 years. These exposures occur as either endemic (exposure to the naturally fluoridated drinking water) or industrial (e.g. exposure to the cryolite dust) (Fejerskov, 1996; Whitford, 1996). Besides the dose and duration of fluoride exposure, the development of skeletal fluorosis is influenced by various other factors. The most common are age, physical activity, kinetics of bone remodeling, nutritional status and renal insufficiency (Kleerekoper, 1996). Epidemiological studies of bone mineral density have not detected changes consistent with skeletal fluorosis resulting from the consumption of drinking water containing fluoride at the concentrations considered optimal for caries prevention.

Report of the expert panel for water fluoridation review. (March 1998). City of Calgary, and Calgary Regional Health Authority: Appointed by the Standing Committee on Operations and Environment.

Page 9: When fluoride accumulates in the skeleton to high levels (usually above 5000 ppm in bone ash) a clinical problem of skeletal fluorosis can be documented. At very high levels (usually well above 5000 ppm) of fluoride accumulation, patients may have a crippling osteo-arthritis-like syndrome that is attributed to the fluoride stimulation of mineral deposition around the joints and probable multiple micro-fractures in bones adjacent to the joints due to fluoride inhibition of normal mineralization. There is a concern that this level of fluorosis might occur in subjects with a high lifetime intake of fluoride. As we age, our ability to remove fluoride from our body (excretion in the urine) declines, so a theoretical risk in the aged population occurs in areas where water fluoridation is present. Early studies of fluoride content in bone autopsy specimens from communities with higher levels of water fluoride than used in Calgary (greater than 1.5 ppm) have shown some individuals had bone levels in the range, which has been associated with skeletal fluorosis (over 5000 ppm in bone ash) (Amala et al., 1985). I know of no reported cases of skeletal fluorosis that can be related solely to the consumption of artificially fluoridated water at 1 mg/L or less.

The Lord Mayor's taskforce on fluoridation – final report. (1997). Brisbane, Australia: Brisbane City Council.

Page 51: Approximately 50% of ingested fluoride is excreted by the kidneys within 24 hours, a small amount is stored in the teeth, and rest is mainly deposited in the skeleton. Exposure to high levels of fluoride can lead to skeletal fluorosis. This condition produces pain, stiffness and immobility in joints and can lead to more serious neurological disorders. There have been no reports of skeletal fluorosis attributable to water fluoridation in Australia and, overseas, most reports have been linked to sustained high levels of exposure in areas where water fluoride levels are naturally very high or in workers who are occupationally exposed to fluoride. However, no systemic research on skeletal fluorosis has been carried out in Australia, and NHMRC have acknowledged that it would not be surprising if there were undetected cases. The review concluded that it was possible that certain individuals, for instance patients under going dialysis for renal disease, might have a slightly increased risk of skeletal fluorosis.

Natick Fluoridation Study Committee. (1997). Should Natick fluoridate?: A report to the town and Board of Selectmen. (On-line).

Pages 32-33: Osteofluorosis is a complicated disease with a number of stages. The first two stages are pre-clinical, that is, the patient feels no symptoms but changes have taken place in the body. In the first pre-clinical stage,

biochemical changes occur in the blood and bone composition; in the second stage histological changes can be observed in bone biopsies. Some experts call these changes harmful because they are precursors of more serious conditions. Other experts say they are harmless (Hileman, 1988). Most admit that the effects of long-term ingestion of fluoridated water on bone are poorly understood (Hileman, 1988).

The clinical stages of osteofluorosis includes pain in the bones and joints, muscle weakness, fatigue, calcification of ligaments and bone spurs. Most experts in skeletal fluorosis agree that ingestion of 10-20 mg/day for 10-20 years or more can cause crippling skeletal fluorosis and doses as low as 2 – 5 mg/day over the same time period can cause the pre-clinical stages. (Hileman, 1988). Moreover, the total quantity of fluoride ingested is the single most important factor in determining the clinical course of osteofluorosis (Ad hoc committee, 1991). The severity of the symptoms correlates directly with the level and duration of exposure. For almost 40 years, investigators in the US Public Health Service reports that:

“Radiographic changes in bone indicative of skeletal fluorosis, changes in bone mass, and effects on skeletal maturation were not observed at water fluoride concentrations of 1.2 mg/L for 10 years and from 3.3 – 6.2 mg/L for a lifetime (Hodge & Smith, 1981; Sowers et al, 1986; Schlesinger et al., 1956; McCauley & McClure, 1954). In a survey of 170,000 radiographs of patients living in Texas and Oklahoma with water fluoride levels between 4 - 8 mg/L, Stevenson & Watson (1957) found 23 cases of radiographic osteosclerosis, but no evidence of skeletal fluorosis.”

Nevertheless, large numbers of people in Japan, China, India, the Middle East and Africa have been diagnosed with skeletal fluorosis (Hileman, 1988). In India, Tanzania and South Africa, crippling forms of skeletal fluorosis have been reported in pediatric age groups as well (Ad hoc committee, 1991).

Topic: ENAMEL (DENTAL) FLUOROSIS

Major “Tier One” Reviews (United States, World Health Organization, & York)

Medical Research Council. Medical Research Council working group report: water fluoridation and health. (September 2002).

Pages 19-20: Dental fluorosis is a form of developmental defect of tooth enamel. Histologically it presents 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 about 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 US and the risk of fluorosis correspondingly greater for any given water fluoride concentration (Murray, 1986).

Relevant studies. In the US, 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 US. 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/3) ^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: EY 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 and 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 US. However, studies have suggested that 7 to 30% 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>

Research recommendations. There are discrepancies between the dental fluorosis data reported by the York Review and recent data from the US 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 these two aspects. Further methodological work is needed to validate the Thystrup-Fejerskow (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 measure.

Centers for Disease Control and Prevention. (2001). Recommendations for using fluoride to prevent and control dental caries in the United States (MMWR Recommendation Report #14, August 17, 2001). Atlanta, GA: CDC Epidemiology Program Office.

Pages 6-7, 11-12: Concerns regarding the risk for enamel fluorosis are limited to children aged ≤ 8 years; enamel is no longer susceptible once its pre-eruptive maturation is complete (IOM, 1997). Fluoride sources for children aged ≤ 8 years are drinking water, processed beverages and food, toothpaste, dietary supplements that include fluoride (tablets and drops), and other dental products.

The very mild and mild forms of enamel fluorosis appear as chalklike, lacy markings across a tooth's enamel surface that are not readily apparent to the affected person or casual observer (Dean, 1942). In the moderate form, >50% of the enamel surface is opaque white. The rare, severe form manifests as pitted and brittle enamel. After eruption, teeth with moderate or severe fluorosis might break away, resulting in excessive wear of the teeth. Even in its severe form, enamel fluorosis is considered a cosmetic effect, not an adverse functional event (USPHS, 1991; IOM, 1997; Kaminsky et al., 1990; Clark et al., 1993).

When enamel fluorosis was first systemically investigated during the 1930s and 1940s, its prevalence was 12%-15% for very mild and mild forms and zero for moderate and severe forms among children who lived in communities with drinking water that naturally contained 0.9-1.2 ppm fluoride (Dean, 1942). Although the prevalence of this condition in the United States has since increased (USPHS, 1991; Clark, 1994; Szupnar & Burt, 1987), most fluorosis today is of the mildest form, which affects neither cosmetic appearance nor dental function. The increased prevalence in areas both with and without fluoridated community drinking water indicates that, during the first 8 years of life, the total intake of fluoride from all sources has increased for some children. (USPHS, 1991). The 1986-87 National Survey of Dental Caries in U.S. School Children (the most recent national estimates of enamel fluorosis prevalence) indicated that the prevalence of any enamel fluorosis among children was 22%-23% (range: 26% of children aged 9 years to 19% of those aged 17 years) (Brunelle, 1987; Heller et al., 1997). Almost all cases reported in the survey were of the very mild or mild form, but some cases of the moderate (1.1%) and severe (0.3%) forms were observed. Cases of moderate and severe forms occurred even among children living in areas with low fluoride concentrations in the drinking water (Heller et al., 1997). Although this level of enamel fluorosis is not his is not considered a public health problem (Hutton et al., 1951) prudent public health practice should seek to minimize this condition, especially moderate to severe forms. Research into the causes of enamel fluorosis has focused on identifying appropriate risk factors (Pendry et al., 1994; Osuji et al., 1988; Pendry et al., 1989; Pendry, 1995).

Enamel fluorosis occurs among some persons in all communities, even in communities with a low natural concentration of fluoride. During 1930-60, US studies documented that, in areas with a natural or adjusted concentration of fluoride approximately 1.0 ppm in the community drinking water, the permanent teeth of 7%-16% of children with a lifetime residence in those areas exhibited very mild or mild forms of enamel fluorosis (Dean,

1942; Ast et al., 1956; Russell, 1962). Before 1945, when naturally fluoridated drinking water was virtually the only source of fluoride, the moderate and severe forms of this condition were not observed unless the natural fluoride concentration was ≥ 2 ppm (Dean, 1942). The likelihood of a child developing the mild forms of enamel fluorosis might be higher in a fluoridated area than in a non-fluoridated area, but prevalence might not change in every community (Lewis & Banting, 1994; Kumar & Swango, 1999). The most recent national study of this condition indicated that its prevalence had increased in both fluoridated and non-fluoridated areas since the 1940s, with the relative increase higher in non-fluoridated areas. In communities with drinking water containing 0.7-1.2 ppm fluoride, the prevalence was 1.3% for the moderate form of enamel fluorosis and zero for the severe form; thus few cases of enamel fluorosis were likely to be of cosmetic consequence (USPHS, 1991; Heller et al., 1997). Because combined fluoride intake from drinking water and processed beverages and food by children in fluoridated areas has reportedly remained stable since the 1940s, the increase in fluoride intake resulting in increased enamel fluorosis almost certainly stems from the use of fluoride-containing dental products by children aged <6 years (IOM, 1997).

Two studies reported that extended consumption of infant formula beyond age 10-12 months was a risk factor for enamel fluorosis, especially when formula concentrate was mixed with fluoridated water (Pendry et al., 1994; Osuji et al., 1988). These studies examined children who used pre-1979 formula (with higher fluoride concentrations). Whether fluoride intake from formula that exceeds the recommended amount during only the first 10-12 months of life contributes to the prevalence or severity of enamel fluorosis is unknown.

Fluoride concentrations in drinking water should be maintained at optimal levels, both to achieve effective caries prevention and because changes in fluoride concentration as low as 0.2 ppm can result in a measurable change in the prevalence and severity of enamel fluorosis (Evans & Stamm, 1991; Szupnar & Burt, 1988).

Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. (2001 draft and 1993). Toxicological profile for fluorides, hydrogen fluoride, and fluorine.

Pages 80-81: There is some evidence that levels of fluorosis have increased due to the multiple, widespread sources of fluoride in food processed with fluoridated water and dentifrices containing fluoride, in addition to the water of fluoridated communities. Comparison of fluorosis levels in 21 cities with fluoride ranging (0.4 to 2.7 ppm that were surveyed by Dean in the 1940s, and studies of dental fluorosis in 21 cities that were conducted in the 1980s found that both the prevalence and the severity of dental fluorosis were correlated with the level of fluoride in the drinking water (DHHS, 1991). During this 40 year period, the prevalence of fluorosis in areas with <0.4 ppm fluoride increased from <1 to about 6%; nearly all of the increase was in the very mild and mild categories. Both the prevalence and severity of fluorosis increased in communities with 0.7-1.2 ppm fluoride, with prevalence increasing from about 13 to about 22%. Most of the increase was in the very mild and mild categories, which increased from 12.3 to 17.7%, and from 1.4 to 4.4% of the population respectively. The combined prevalence of the severe and moderate categories increased from 0.0 to 0.9%. While there were some differences between the studies in the 1940s and those in the 1980s, such as the subject population and examination conditions, they do not effect overall trends. Although total fluoride intake was not measured, these studies indicate that intake has increased since the 1940s, because fluorosis levels increased for all water fluoride levels.

Fluorosis levels in 1985 in communities with fluoride levels at about 1,2,3 and 4 ppm were compared with levels of fluorosis in the same communities in 1980 (Heifetz et al., 1988). Both examinations included 8-10 year old and 13-15 year old children. The 13-15 year old children in the follow-up study had also participated in the initial study. While there were no marked changes in fluorosis levels in 8-10 year old children, both the prevalence and severity increased in the 13-15 year old children. Increases in the 1ppm communities were mostly in the category of barely visible white spots. However, the percentages of labial surfaces of incisors and canines from children in the 2 ppm group that had brown mottling increased from 0 to 7.6%. Less marked increase in mottled and pitted teeth were seen in the higher dosage groups. The increased levels of fluorosis were attributed to increased fluoride exposure from multiple sources.

While drinking water fluoride levels ranging from 0.7-3.0 ppm can reduce the incidence of dental caries, susceptibility to caries can increase at higher fluoride levels. Adolescents consuming water containing 5 ppm fluoride since birth were evaluated for fluorosis and prevalence of caries. The prevalence of dental fluorosis was 100%, with the 182 subjects showing effects ranging from mild to severe (Mann et al., 1987).

NHS Centre for Reviews and Dissemination, University of York. (2000). A systematic review of public water fluoridation. York, UK: York Publishing Services Ltd.

Page xiii, executive summary: Dental fluorosis was the most widely and frequently studied of all negative effects. The fluorosis studies were largely cross-sectional designs, with only 4 before-after designs. Although 88 studies of fluorosis were included, they were of low-quality. The mean validity score for fluorosis was only 2.8 out of 8. All but one of the studies were of evidence level C. Observer bias may be of particular importance in studies assessing fluorosis. Efforts to control for the effects of potential confounding factors, or reducing potential for observer bias was uncommon.

As there may be some debate about the significance of a fluorosis score at the lowest level of each index being used to define a person as 'fluorosed', a second method of determining the proportion 'fluorosed' was selected. This method describes the number of children having dental fluorosis that may cause 'aesthetic concern.'

With both methods of identifying the prevalence of fluorosis, a significant dose-response relationship was identified through a regression analysis. The prevalence of fluorosis at a water fluoride level of 1.0 ppm was estimated to be 48% (95% CI 40-57) and for fluorosis of aesthetic concern it was predicted to be 12.5% (95%CI 7.0-21.5). A very rough estimate of the number of people who would have to be exposed to water fluoride levels of 1.0 ppm for one additional person to develop fluorosis of any level is 6 (95% CI 4-21), when compared with a theoretical low fluoride level of 0.4 ppm. Of these approximately one quarter will have fluorosis of aesthetic concern, but the precision of these rough estimates is low. These estimates only apply to the comparison of 1.0 ppm to 0.4 ppm, and would be different if other levels were compared.

Discussion, page 45: Fluorosis was the most widely and frequently studied of all the possible adverse effects considered. The fluorosis studies used were cross-sectional designs, with a few before-after designs (again using different groups of people at each time point). The mean validity score was only 2.8 out of 8 and all but one of the studies was evidence level C. Observer bias may be of particular importance in studies assessing fluorosis. Efforts to control for potential confounding factors, or reducing potential observer bias were infrequently undertaken. Seventy-two of 88 studies did not use any form of blinding by the assessor, and 50 of 88 did not control for confounding factors, other than by simple stratification by age or sex.

The primary fluorosis analysis was based on prevalence of 'fluorosed' people, including any degree of fluorosis. A conservative approach for defining fluorosis was used in this analysis, in that the 'questionable' category in Dean's index was counted as fluorosis. Because there is evidence that very mild forms of fluorosis are not concerning to people (indeed some even preferred photographs of mildly fluorosed teeth) a secondary analysis assessed the prevalence of fluorosis of 'aesthetic concern'.

With both methods of measuring the prevalence of fluorosis, a significant dose-response relationship was identified through the univariate regression analysis. The prevalence of fluorosis at a water fluoride level of 1.0 ppm was estimated to be 48% (95% CI 40-57) for any fluorosis and 12.5% (95% CI 7.0-21.5) for fluorosis of aesthetic concern. The numbers of additional people who would have to be exposed to water fluoride levels of 1.0 or 1.2 ppm for one additional person to develop fluorosis of any level were quite low, 5 or 6 when comparing to a theoretical low fluoride level of 0.4 ppm. For fluorosis of esthetic concern to occur in one additional person, however, the number was 22 at 1 ppm, but the 95% CI included infinity.

The multivariate analysis of fluoride took into account variables potentially contributing to the heterogeneity between studies. This analysis found a statistically significantly higher risk in children with permanent teeth, compared with primary teeth or both types. The multivariate analysis of fluorosis of aesthetic concern confirmed these findings. A sensitivity analysis limiting the range of water fluoride levels entered into the model did not alter the findings in any meaningful way.

The estimated NNT for one extra child to be caries-free was seven (95% CI 5-10), while the NNH for fluorosis is six (95% CI 4-21), with approximately a quarter of these being of aesthetic concern. These estimates are based on comparisons of specific levels of water fluoridation (e.g. <0.7 ppm vs. 0.7 – 1.2 ppm for caries, and 0.4 ppm vs. 1.0 ppm for fluorosis). The numbers would change if different levels of fluoridation were compared.

Committee on the Scientific Evaluation of Dietary Reference Intakes. (1999). Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, D.C.: National Academy Press.

Page 306: Enamel fluorosis is a dose-response effect caused by fluoride ingestion during the pre-eruptive development of the teeth. After the enamel has completed its pre-eruptive maturation, it is no longer susceptible. Inasmuch as enamel fluorosis is regarded as a cosmetic effect, it is the anterior teeth that are of most concern. The pre-eruptive maturation of the crowns of the anterior permanent teeth is finished and the risk of fluorosis is over by 8 years of age (Fejerskov et al., 1977). Therefore, fluoride intake up to the age of 8 years is of most interest. Several reports suggest that enamel in the transitional or early maturation stage of development is most susceptible to fluorosis, which for the anterior teeth, occurs during the second and third years of life (Evans, 1989; Evans and Darvell, 1995; Pendrys and Katz, 1989; Pendrys and Stamm, 1990). Some evidence indicates that the risk of mild enamel fluorosis in the primary teeth is somewhat increased as a result of the relatively high fluoride intake associated with feeding some infant formulas reconstituted with fluoridated water (Larsen et al., 1988).

Fluorosed enamel has a high protein content. This results in increased porosity, which, in the moderate and severe forms, may eventually become stained and pitted (Fejerskov et al, 1977; Kaminsky et al, 1990). Clinically, the milder forms of enamel fluorosis are characterized by opaque striations that run horizontally across the surfaces of the teeth. The striations may become confluent giving rise to white opaque patches, often most apparent on the incisal edges of anterior teeth of cusp tips of posterior teeth (“snow-capping”). Mild fluorosis has no effect on tooth function and may render the enamel more resistant to caries. It is not readily apparent to the affected individual or casual observer and often requires a trained specialist to detect. In contrast, the moderate and severe forms of enamel fluorosis are generally characterized by esthetically objectionable changes in tooth color and surface irregularities. Most investigators regard even the more advanced forms of enamel fluorosis as a cosmetic effect rather than a functional adverse effect (Clark et al., 1993; Kaminsky et al, 1990).

Page 302: Dental fluorosis has a strong dose-response relationship with fluoride intake. Dean (1942) established that the milder forms of enamel fluorosis affected the permanent teeth of 10-12% of permanent residents in communities where the drinking water has a fluoride concentration close to 1.0 mg/liter. The fluoride intake of children with developing teeth in these communities averaged 0.05 mg/kg/day and ranged from 0.02 to 0.10 mg/kg/day. In areas where the water contained low concentrations of fluoride (0.3 mg/L), fewer than 1% of the permanent residents had enamel fluorosis. Mild enamel fluorosis affected about 50% of residents where the water contained 2.0 mg/l of fluoride. At this concentration, a few cases (<5%) of moderate fluorosis were recorded (Dean, 1942). Fluoride intake by most children in these communities would have ranged from approximately 0.08 to 0.12 mg/kg/day. An average, chronic daily fluoride intake of 0.10 mg/kg appears to be the threshold beyond which moderate enamel fluorosis appears in some children. Where the water concentration was 4.0 mg/L, nearly 90% of the residents had enamel fluorosis, and about ½ of the cases were classified as moderate or severe.

Because cosmetic effect of the milder forms of enamel fluorosis are not readily apparent, moderate enamel fluorosis was selected as the *critical adverse* effect for susceptible age groups (infants, toddlers, and children from birth through the age of 8 years). Thus a fluoride intake of 1.0 mg/kg/day was identified as a LOEL for moderate enamel fluorosis in children from birth through the age of 8 years, at which age the risk of developing fluorosis of the anterior teeth is over. Based on a LOAEL of 1.0 mg/kg/day for moderate enamel fluorosis and an uncertainty factor of 1, a Tolerable Upper Intake Level (UL) of 1.0 mg/kg/day was established for infants, toddlers and children through 8 years of age. The extensive epidemiological research conducted in the US during the 1930s and 1940s (Dean, 1942) established, with a high degree of certainty, that a chronic fluoride intake of less than 0.10 mg/kg./day by children at risk of enamel fluorosis was associated with a low prevalence (for example, approximately 10%) of the milder forms of the condition. Based on a UL of 0.10 mg/kg/day of fluoride and a reference weight for infants ages 0-6 months of 7 kg, the UL is 0.7 mg/day. For children ages 7-12 months with a reference weight of 9 kg, the UL is 0.9 mg/day. Based on a UL of 0.10 mg/kg/day of fluoride and a reference weight for children ages 1-3 years of 13 kg, the UL is 1.3 mg/day for children ages 1-3 years. For children ages 4-8 years with a reference weight of 22 kg, the UL is 2.2 mg/day.

Pages 311-312: Prior to the 1960s, the diet, including water, was the only significant source of fluoride. Since then, fluoride ingestion resulting from the use of dental products and fluoride supplements has increased the risk of enamel fluorosis in children. The results of several studies (Kumar et al, 1989; Leverett, 1986; Pendrys & Stamm, 1990; Williams & Zwemer, 1990) have indicated that mild enamel fluorosis in communities with optimally fluoridated water (1.0 mg/L) is now more than twice and prevalent as in the 1930s and 1940s; that is, the prevalence has increased from

an average of about 10% to an average approaching 25%. In communities where the water has a low fluoride concentration (0.3 mg/L or less), the prevalence has increased from <1% to slightly more than 10%. These findings reflect levels of fluoride ingestion by some children with developing teeth that are higher than heretofore.

Moreover a recent national survey (Wagener et al., 1995) found that dietary fluoride supplements were used by 15% of children under 2 years of age, 16% by those 2-4 years of age, and 8% by those 5-17 years of age. In their study of infants born in Iowa City, a university community with a high socioeconomic status, Levy et al. (1995) reported that from 19-25% of infants between the ages of 6 weeks and 9 months were given fluoride supplements. Pendrys & Morse (1990) and Levy & Muchow (1992) are among those who have found that supplements are often prescribed at the wrong dosage and in areas where they are not recommended because the water is already fluoridated at recommended levels. Recommendations have been made to reduce fluoride from non-dietary sources (NRC, 1993; USPHS, 1991; Workshop Reports, 1992).

World Health Organization. (1994). WHO technical report series #846: Report of a WHO expert committee on oral health status and fluoride use. Geneva, Switzerland: World Health Organization.

Pages 14-15: Studies in the United States of America during the late 1930s and early 1940s in communities with varying levels of naturally occurring fluoride in the drinking-water found that, at 1 mg of fluoride per liter, the reduction in the prevalence of dental caries was approximately 50%. This reduction was associated with very mild forms of fluorosis in a small percentage of the population – about 10% (Dean, 1942). At the time this low level of fluorosis was deemed not to represent a public health problem; if it was even noticed, it was considered acceptable and far preferable to the severe dental caries it largely replaced. It is worth noting that this compromise – that is the priority accorded to caries over fluorosis – is found with a number of fluoride procedures.

In the past 30 years our understanding of the method of action of fluoride in the prevention of dental caries has changed; it is now accepted that it is mainly post-eruptive. Achieving the best possible caries prevention usually requires the use of population-based programmes such as adding fluoride to drinking-water or salt or the widespread use of fluoride toothpastes. The question therefore arises whether the maximum caries preventive effect can be achieved without the appearance of some degree of very mild fluorosis in the target population. In communities served with optimally fluoridated water supplies a small proportion of the population will continue to be affected by very mild fluorosis, evident as diffuse white lines and patches, which is not aesthetically damaging and which usually cannot be seen by the untrained eye. In communities where additional sources of fluorides are available, such as fluoridated toothpaste, which can be swallowed by young children, the prevalence of unaesthetic forms of fluorosis will increase. For example, in many parts of the United States of America much of the noticeable rise in the prevalence of very mild fluorosis can be accounted for by physicians prescribing fluoride supplements for children resident in fluoridated communities, a clearly inappropriate procedure. Over the past 20 years different indices have been developed for recording the first, barely perceptible diffuse white lines in enamel that are associated with fluoride ingestion, and it is now feasible to measure these changes reliably in epidemiological studies. Dental fluorosis is being regularly monitored in many communities.

National Research Council. (1993). Health effects of ingested fluoride. Washington, D.C.: National Academy Press.

Pages 4-6: One side effect of too much fluoride ingested in early childhood while teeth are forming, however, is dental fluorosis; the enamel covering of the teeth fails to crystallize properly, leading to defects that range from barely discernible to severe brown stain, surface pitting, and brittleness. Fluoride intake by children 2-5 years old is particularly important because the anterior (front) permanent teeth are at the early-maturation stage, during which they are particularly susceptible to fluoride-induced changes. Dental fluorosis also is a dose-response condition: the greater the fluoride intake during tooth development, the more severe the dental fluorosis. Depending upon the amount and time (relative to tooth development) of fluoride absorbed, severity of dental fluorosis can range from barely discernible to severe manifestations of stained and pitted tooth enamel. PHS's recommended fluoride concentration in drinking water, 0.7-1.2 mg/L, was designed to maximize prevention of dental caries while limiting the prevalence of dental fluorosis to about 10% of the population, virtually all of it mild to very mild.

A 1991 report from the Public Health Service of the US Department of Health and Human Services compiled the results of independent investigations conducted during the 1980s on dental fluorosis in 24 cities and compared them with a series of PHS surveys conducted during the late 1930s and early 1940s in 21 cities. That comparison showed that the prevalence of dental fluorosis, most of it mild to very mild, had increased. The 1980s data showed that the mean prevalence of dental fluorosis in four cities with optimally fluoridated water supplies was around 22% (17% very

mild, 4% mild, 0.8% moderate, and 0.1% severe). In another city with water fluoride concentration in the range of 1.8 – 2.2 mg/L, dental fluorosis prevalence was 53% (23% very mild, 17% mild, 8% moderate, and 5% severe). The data from the PHS report also showed that the greatest relative increase in fluorosis prevalence since the early studies was in communities with very low water fluoride concentrations, demonstrating the influence of sources of fluoride other than water. Those sources make it difficult to estimate fluoride exposure; they represent a source of possible error in estimating fluoride intake in studies of the relation between fluoride exposure and dental fluorosis. Moreover there is disagreement on whether dental fluorosis (even moderate-to-severe dental fluorosis, in which substantial root enamel is affected and dental treatment might be required) is a cosmetic problem or an adverse health effect.

In general, the evidence supports the conclusion that fluoridation at the recommended concentrations, in the absence of fluoride from other sources, results in a prevalence of mild-to-very mild (cosmetic) dental fluorosis in about 10% of the population and almost no cases of moderate or severe dental fluorosis. At five or more times the recommended concentration, the proportion of moderate-to-severe dental fluorosis is substantially higher.

Committee to Coordinate Environmental Health and Related Programs, USPHS. (1991). Review of fluoride: Benefits and risks: Report of the subcommittee on fluoride of the EHPC. Public Health Service: Department of Health and Human Services.

Page 5, executive summary: Although the precise mechanism that causes dental fluorosis is unknown, the likelihood of dental fluorosis is related directly to the level of fluoride exposure during tooth development. The clinical spectrum of dental fluorosis varies from symmetrical whitish areas on teeth (very mild) to secondary, extrinsic, brownish discoloration and varying degrees of pitting of the enamel (severe dental fluorosis). Among children, the prevalence of moderate and severe forms of dental fluorosis is estimated to be 1.3% nationally. Although fluorosis has historically been considered to be a cosmetic problem, these forms of dental fluorosis do not produce adverse dental health effects, such as tooth loss or impaired tooth function.

In the 1940s and 1950s, the major sources of fluoride were from drinking water and food. Since then, additional sources of fluoride have become available, including processed beverages and food, dental products containing fluoride (e.g. toothpastes and mouth rinses), and fluoride dietary supplements. Inappropriate use of these products can substantially increase total fluoride intake.

In the 1940s, approximately 10% of the population had fluorosis when the concentration of fluoride found naturally in the drinking water was about 1 ppm. Since the 1950s, in non-fluoridated areas, the total prevalence of dental fluorosis has clearly increased. During the same period, in areas where water fluoride concentrations have remained in the optimal range (about 1 ppm fluoride), the total prevalence of dental fluorosis may have increased. Increases in the prevalence of dental fluorosis suggest that total fluoride exposure is increasing. Because dental fluorosis does not compromise oral health or tooth function, an increase in dental fluorosis does not represent a public health concern; however, it indicates that total fluoride exposure may be higher than that necessary to prevent tooth decay. In general, prudent public health practice dictates using no more than the amount necessary to achieve a desired effect.

Summary page 62 of full report: Human dental fluorosis is associated with high tissue fluoride concentration during tooth formation. The greater the fluoride exposure during tooth development, the greater the likelihood of dental fluorosis. The actual concentration of fluoride that correlated with an observed clinical presentation, in a given individual, is difficult to quantify. The prevalence and severity of fluorosis depend on: 1) the amount, concentration, and duration of exposure to fluoride; 2) the stage of tooth development; 3) individual variations in susceptibility; and 4) certain environmental variables.

Overall, dental fluorosis remains more prevalent in fluoridated than non-fluoridated areas. Dental fluorosis appears to have increased in both non-fluoridated and fluoridated communities, but has increased much more in non-fluoridated or low fluoride areas. Apparently, in non-fluoridated areas over the period 1939 to about 1980, increases in very mild and mild forms of dental fluorosis have occurred. Total prevalence and intensity of dental fluorosis may have increased in optimally fluoridated areas over this same time period. Virtually all of the increase observed in optimally fluoridated areas since Dean's time has occurred in the very mild and mild categories. If moderate dental fluorosis has increased, the increase is minimal and has been most pronounced between the water fluoride ranges of 1.8-2.2 mg/L. During this period of time the prevalence of severe forms of dental fluorosis continues to be very low in optimally fluoridated areas.

In comparison of cross-sectional studies from 1980 and 1985 in the same midwestern communities, investigators reported an increased prevalence of dental fluorosis by tooth surface (rather than by individual), which may be due in part to increased fluoride ingestion among children. Apparently, the increased ingestion began in the early 1970s,

and since then the total fluoride intake has changed very little. Evidence from 1980 and 1985 surveys identified increases in percentages of tooth surfaces with dental fluorosis at optimum, 2X, 3X, and 4X optimal levels of water fluoride in children 13-15 years of age and at optimal levels in children 8-10 years. There may have been a slight increase in moderate to severe forms of dental fluorosis in some children 13-15 years old in communities fluoridated at the 2X, 3X, and 4X optimal levels. The study was geographically restricted to four areas of Illinois, so the general applicability of the study is unknown.

Factors found to be associated with an increase in the reported prevalence of dental fluorosis include the daily – and possibly inappropriate – use of dietary fluoride supplements, the use of fluoride containing toothpaste before a child is 24 months of age, and the use by children beyond 13 months of age of powdered and concentrated forms of infant formula reconstituted with fluoridated water. Because of changes in manufacturing practices of infant foods since 1978, the risks associated with these products may no longer be operative.

In most studies in which the risk of developing dental fluorosis has been assessed, investigators have focused almost exclusively on a single risk factor, that is on a single source of fluoride and have not controlled for multiple sources. The effect on dental fluorosis of multiple risk factors or of the simultaneous use of multiple fluoride modalities, remains largely unknown.

International Programme on Chemical Safety. (1984). Environmental health criteria 36: Fluorine and fluorides. Geneva, Switzerland: World Health Organization.

Pages 81-83: Dental fluorosis is a disturbance affecting the enamel during formation, hence all damage occurs before the eruption of the teeth. The level of fluoride induced changes that would be considered aesthetically objectionable is debatable.

The minimal daily fluoride intake in human infants that may cause very mild or mild fluorosis in human beings has been estimated to be about 0.1 mg per kg body weight (Forsman, 1977). This figure was derived from examination of 1094 children from areas with water-fluoride concentrations of 0.2-2.75 mg/liter. It is in agreement with the reported 0.1-0.3 mg per kg body weight necessary to initiate fluorosis in cows.

The results published by Dean and co-workers have been confirmed by many studies in various temperate parts of the world, as reviewed by Myers (1978), i.e. fluorosis is of a very mild or mild character in areas with drinking-water naturally containing fluoride levels of up to 1.5-2.0 mg/liter, severe fluorotic defects with disfiguring appearance are to be found at higher fluoride levels.

It is sometimes difficult or almost impossible to discriminate between fluorosis and other enamel disturbances (Jackson, 1961; Forrest & James, 1965; Goward, 1976; Mervi 1977; Small & Murray, 1978; Murray & Shaw 1979). Opacities similar to fluorotic opacities are also seen in low fluoride areas and many etiological factors other than fluoride have been implicated (Small & Murray, 1978).

Small & Murray (1978) concluded: Although a high concentration of fluoride in drinking water is one factor, it is extremely difficult to decide just how many cases of “enamel fluorosis occur in endemic areas and how many defects are due to other etiological factors.”

Localized enamel defects are reported to be more frequent in low-fluoride areas than in areas with optimal water fluoridation (Zimmerman, 1954; Ast et al., 1956; Forrest, 1956; Forrest & James, 1965; Al-Alousi et al., 1975; Forsman 1977). One of the explanations offered is that part of the difference may be due to the greater amount of caries-induced inflammation in temporary teeth in low-fluoride areas, as such conditions have been found to disturb the mineralization of underlying permanent teeth. It has also been suggested that a certain amount of fluoride is necessary for the proper organization and crystallization of enamel. As a consequence of higher water consumption, the frequency and severity of dental fluorosis increases with increasing mean maximum temperature (Galaghan et al., 1957; Richards et al., 1967; Gobovich & Ovurutskiy, 1969).

As the community index of fluorosis increases, caries prevalence decreases until the destructive forms of fluorosis, scores of 4 and 5 on Dean's index, become prevalent. Under the latter conditions, an increase in caries may occur, associated with loss of integrity of enamel and exposure of underlying dentine. However, under these situations, the lesions usually progress slowly and frequently become arrested (Barnes, 1983).

Other Reviews

(examples of municipal or territorial reviews of the water fluoride issue)

Locker, David. (1999). Benefits and risks of water fluoridation. An update of the 1996 federal-provincial sub-committee report. Prepared under contract for the Public Health Branch, Ontario Ministry of Health, First Nations Inuit Health Branch, Health Canada. University of Toronto: Community of Dental Health Services Research Unit, Faculty of Dentistry.

Pages 35-43: Recent reviews have suggested that the prevalence and severity of dental fluorosis has increased in both fluoridated and non-fluoridated communities with the later exhibiting the largest increase of all (Lewis and Banting, 1994; Clark 1994). A review by Clark (1994) of North American studies published prior to 1994 indicated that prevalence ranged from 35-60% in fluoridated communities and from 20-45% in non-fluoridated communities. These increases have been attributed to the consumption of fluoride from sources other than community water supplies (Lewis and Banting, 1994). Although they are largely confined to the so-called “very mild” and “mild” categories of dental fluorosis the increases are cause for concern. The rationale underlying this concern is that fluorosis at this level is discernible by children aged 10 years and over and can lead to embarrassment, self-consciousness and a decrease in satisfaction with the appearance of the teeth (Spencer et al., 1996). This work confirms and expands previous surveys which have shown that lay people can detect fluorosis and both professionals and lay people view the more severe forms as having negative consequences for children (Riordan, 1993; Clark, 1993; Hawley et al., 1996).

The most recent estimates of the prevalence of fluorosis in both fluoridated and non-fluoridated communities are found in table 9-11. These studies suffer from the same design and methodological limitations as the studies of the effectiveness of water fluoridation discussed earlier.

North American studies, which confined their estimates to children who were life-long residents of fluoridated and non-fluoridated communities respectively, reported prevalence rates of 20-75% for the former and 12-45% for the latter.

Two U.S. studies using repeated cross-sectional designs were undertaken by the same investigators and provide the best recent estimates of trends in fluorosis. Jackson et al. (1999) studied 7-14 year old children who were life-long residents of a fluoridated and a non-fluoridated city. In the fluoridated city the proportion of children who had a TSIF score of 1 or more increased from 45% in 1992 to 65% in 1994 (NS). In the non-fluoridated city there was a significant increase from 18 to 33%. Kumar and Swango (1999) also compared 7 to 14 year old children who were life-long residents of a fluoridated community, Newburgh, and a non-fluoridated community, Kingston. Dean’s CFI indicated a significant increase in both communities between 1986 and 1995; from 7.9 to 18.6% in the former and from 7.4 to 11.7% in the latter. The difference in rates between the studies is probably due to the fact that Dean’s CFI has a “questionable” category, which is categorized as “normal” for the purpose of calculating prevalence estimates.

The conventional way of estimating the contribution of water fluoridation to dental fluorosis is by the use of relative risks and attributable risk percents (Lewis and Banting, 1994). Relative risks in North American and European studies varied from 1.5 to 2.7, except for one Norwegian study that had a relative risk of 5.4. Attributable risks percents measure the proportion of the fluorosis in those exposed to water fluoridation, which can be attributed to that exposure rather than other sources of fluoride. In North American studies this varied from 40-63% and in the European studies from 33-82%. These studies suggest approximately half of the fluorosis affecting contemporary child populations is the result of water fluoridation and half is the result of exposure to other, discretionary sources of fluoride. However, in some jurisdictions the halo effect could potentially affect these crude estimates (Lewis and Banting, 1994).

Two Canadian studies are worth highlighting here. Clark et al. (1994) used the TSIF to compare life-long residents of a fluoridated and non-fluoridated community in British Columbia. Among samples of children aged 6-14 years, the prevalence of fluorosis (TSIF ≥ 1) was 75% in the former and 45% in the latter (RR = 1.7; AR% = 41%). Brothwell and Limeback (1999) examined grade 2 students living in a non-fluoridated rural area in Ontario, approximately 10% of whom lived in homes where the water was naturally fluoridated to 0.70 mg/L or more. There was no significant differences in the prevalence of fluorosis among students from fluoridated and non-fluoridated homes when judged by a TSIF score of 1 (31% vs. 25%). However, there was a significant difference among the proportions with TSIF scores of 2 or more (18.8% vs. 4.8% respectively; RR = 3.9; AR% = 77%). This latter study suggests that water fluoridation may play a more prominent role in moderate to severe fluorosis than in fluorosis overall.

The risks associated with discretionary use of fluorides in both fluoridated and non-fluoridated communities have been addressed in a number of recent studies. In addition two reviews (Warren & Levy, 1999 and Ismail and Bandecker, 1999) have been published.

The main risk factors to emerge from the case-control and cross-sectional studies were the use of infant formula, use of fluoride supplements and brushing with fluoridated toothpaste early in life. The two reviews confirm the etiological role of fluoridated toothpaste and fluoride supplements with respect to fluorosis.

Page 43, summary: Current studies support the view that dental fluorosis has increased in both fluoridated and non-fluoridated communities, North American studies suggest rates of 20-75% in the former and 12-45% in the latter. Although largely confined to the 'very mild' and 'mild' categories of the condition, they are of concern insofar as they are discernible to the lay population and may impact on those so affected. Although about half the fluorosis in contemporary child populations living in fluoridated communities can be attributed to fluoride from discretionary sources, efforts to reduce exposure to these sources may not be successful.

Report of the expert panel for water fluoridation review. (March 1998). City of Calgary, and Calgary Regional Health Authority: Appointed by the Standing Committee on Operations and Environment.

Page 16: Fluorosis is a side-effect of excessive fluoride ingested during the process of tooth formation. It cannot occur after the teeth have fully developed. Excessive fluoride leads to improper crystallization of enamel with a less tightly formed crystalline lattice. This can lead to a varying degree of enamel surface porosity. In mild cases it causes various degrees of mottling which are often not visible to untrained eyes. In severe cases it leads to pitting of the enamel surface and enamel fragility. It is known that an intake of even a trace amount of fluoride can lead to a mild fluorosis in some individuals. Since normal human diet always contains small amounts of naturally occurring fluoride, there will always be some dental fluorosis in a population.

In North America the vast majority of dental fluorosis is of very mild to mild types. The moderate and severe types which over the years become discolored as result of taking up stain from foods, beverages and tobacco smoke are not common.

The prevalence of dental fluorosis has increased during the last several decades in both fluoridated and non-fluoridated communities. In fact this increase has been more marked in some non-fluoridated areas and has been attributed to the inappropriate use of fluoride supplements (drops, tablets, dental products) as well as the consumption of beverages and foods prepared with fluoridated waters (Pendry et al., 1990).

Pendry and Stamm (1990) and Lewis and Banting (1994) have reviewed the literature on enamel fluorosis. Both studies concluded that there is a strong association between mild to moderate fluorosis and the use of fluoride supplements in early childhood. Whereas during the past several decades, there has been a 33% increase in the prevalence of enamel fluorosis in fluoridated communities, the non-fluoridated communities have experienced a 1000% increase during the same period. Obviously the fluorosis prevalence in the fluoridated communities has also been affected by the inappropriate use of fluoridated dentifrices.

In a more recent publication Pendry (1995) reported the results of his well-designed retrospective case-control study of middle-school-aged children who grew up in "optimally" fluoridated communities. He calculated that about 15% of fluorosis in these communities can be attributed to inappropriate use of supplements (drops and tablets) and about 71% to the inappropriate use of fluoridated dentifrices during the children's first 8 years of life.

It should not come as a surprise that there is a greater prevalence of dental fluorosis in some non-fluoridated communities since fluoride drops and tablets are more frequently used in those communities. When these children use (and swallow) excessive amounts of fluoridated toothpaste and consume beverages and food prepared with fluoridated water, their total fluoride ingestion becomes greater than that of children in fluoridated communities (Pendry et al., 1990).

Given the availability and indiscriminate use of fluoridated dental products, it is clear that, at the present time young children can be exposed to excessive amounts of fluoride, which is unnecessary for maintaining their dental health.

Page 30, summary – majority opinion: Dental fluorosis occurs when total fluoride is too high during the formation of enamel on children's teeth. Because the total intake of fluoride from all sources is increasing, more fluorosis is being observed although much of it is of the mild forms, which are only apparent to the trained eye or upon very close inspection. The Panel recommends that health authorities pay more attention to identifying uncontrolled

sources of fluoride, especially due to children swallowing high fluoride toothpaste. Reducing uncontrolled sources of fluoride would be a more effective means of reducing dental fluorosis than eliminating fluoridation of water.

The Lord Mayor's taskforce on fluoridation – final report. (1997). Brisbane, Australia: Brisbane City Council.

Page 51-52: Dental fluorosis is a specific disturbance of tooth formation caused by excessive intake of fluoride during the formative period of the dentition. The manifestations depend on the peak concentrations achieved in the blood following exposure to fluoride (usually by ingestion), the duration of exposure and the age of the subject. Clinically, dental fluorosis is characterized by lusterless, opaque white patches in the enamel, which may become striated, mottled and/or pitted in more severe forms. The opaque areas may become stained yellow to dark brown. The severity of fluorosis is graded from very mild to severe.

The critical period for developing fluorosis is during the maturation period of tooth enamel, which for the cosmetically important maxillary (upper) anterior teeth is the second and third year of life. Fluorosis is considered probable following intakes of 0.1 mg F/kg body weight during infancy (Forsman, 1977). More recent reports have suggested a lower threshold: 0.03-0.10 F/kg/mg body weight has been suggested as borderline, at least for European children (Fejerskov et al., 1987; Baelum et al., 1987).

In communities receiving artificially fluoridated water prior to the widespread use of fluoride toothpaste, most fluorosis was of the questionable or very mild variety. No treatment was considered necessary for either questionable or very mild fluorosis, as patients were usually unaware of both from a cosmetic standpoint. Mild and moderate fluorosis were more common in situations where toothpaste was swallowed, tablets ingested, or water levels contained high naturally occurring levels of fluoride.

Natick Fluoridation Study Committee. (1997). Should Natick fluoridate?: A report to the town and Board of Selectmen. (On-line).

Pages 30-31, summary and conclusions: Excessive fluoride intake by children causes a toxic dental condition known as dental fluorosis which is marked by visible mottling/discoloring of tooth enamel, pitting of the enamel and disturbed tooth shape. Dental fluorosis occurs during early childhood while the baby and permanent teeth and tooth enamel are still being mineralized and before they erupt in the mouth. The severity of the dental fluorosis is directly proportional to the fluoride ingested in excess of 0.03 mg to 0.07 mg fluoride/kg of body weight/day. The ultimate result is the increased porosity of the teeth and, in extreme cases, loss of afflicted teeth. The prevalence of dental fluorosis is increasing in communities that are “optimally fluoridated” and in those with fluoride deficient doing (sic) water because of the ubiquity of products containing fluoride. However the prevalence and severity of dental fluorosis is greater in “optimally fluoridated” communities than those with fluoride-deficient water. Parents are being advised to protect against excessive fluoride intake by infants and children by carefully regulating their total intake of fluoride. It is anticipated that fluoridation of the Natick water supply to 1 ppm of 1 mg/L will result in dental fluorosis to some degree in at least one child out of every ten. However, if care is not exercised in preventing excessive fluoride intake, 2–3 children out of every ten may develop dental fluorosis. Corrective procedures, when required, can be performed by dental clinicians. However, the cost of teeth rehabilitation will be borne, most likely, by the individuals/parent since dental fluorosis is considered to be a cosmetic defect and therefore is not covered by most insurance plans.

Page 3, findings: Ten to thirty percent (10-30%) of Natick's children will have very mild to mild dental fluorosis if Natick fluoridates its water (up from probably 6% now). Approximately 1% of Natick's children will have moderate or severe dental fluorosis. Dental fluorosis can cause great concern for the affected family and may result in additional dental bills. It should not be dismissed as a “cosmetic” effect.

Topic: OTHER HEALTH EFFECTS

Major “Tier One” Reviews (United States, World Health Organization, & York)

Medical Research Council. Medical Research Council working group report: water fluoridation and health. (September 2002).

Pages 32-36. Fluoride exposure has been postulated to cause a number of health effects. 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).

Immunological effects. Information regarding the allergenic 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.

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.

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 level. 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, i.e., increased Down's syndrome incidence with increased water fluoride level. However, it was noted that these two positive studies have 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 multigenerational 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.

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 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 concentration 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.

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 of Sushella et al. (1993) assessed that 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” (i.e., 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 of Sushella 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 (Sushella 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.

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 (e.g., 0.91ppm), which are ore comparable to the levels in fluoridated water in the US, 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.

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

Thyroid (goiter). The York Review listed three studies in which goiter 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 goiter. 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.

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.

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 (e.g., 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 and therefore reduce the effectiveness of intended caries-preventive dose.

Substances added during the fluoridation process. The UK 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 of Na_2SiF_6 powder required 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.

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, resulted in peak fluoride levels of 150ppm and 51ppm respectively, reduced the pH value of the water and caused copper to be leached from plumbing.

Studies on the leaching of aluminium from cooking utensils at standard fluoride concentration 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.

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.

An experimental study (Valner 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 active and 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.

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.

Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. (2001 draft and 1993).
Toxicological profile for fluorides, hydrogen fluoride, and fluorine.

Note – 2001 draft for public comment was used.

Background information on oral exposure (Page 59): Much of the research on fluoride exposure in humans focused on the ingestion of fluoride through supplemented public drinking water supplies. Additional information comes from studies of areas with high natural fluoride levels. Drinking water levels of other minerals may differ between artificially fluoridated areas and areas with naturally fluoridated high fluoride levels. Much of the data regarding toxic effects of oral exposure to fluoride were obtained from studies using sodium fluoride. Fluoride is often added to water in the form of hydrofluosilic acid, so exposure to this chemical is included in some epidemiological studies. For all forms of fluoride discussed, doses are reported as amount of the fluoride ion.

For the most part, summaries of animal studies cited in this document are not cited here, the intended focus was studies of humans exposed fluoridated water.

All cause mortality (Page 61): A comparison of death rates between US cities with fluoridated water and those with non-fluoridated water found no association between fluoride and increased death rate (Erickson, 1978). It is difficult to draw definitive conclusions from this study because it is limited by dissimilarities between the populations, which led to a need for multiple adjustments.

Respiratory effects (Page 62): No studies were located regarding respiratory effects in humans after oral exposure to fluorine, hydrogen fluoride or fluoride.

Cardiovascular effects (Page 76): In two epidemiological studies, fluoride in the drinking water did not increase the mortality rates from cardiovascular effects. One of these studies was a report of 428,960 people in 18 areas of “high” natural fluoride (0.4->3.5 ppm) in England and Wales and 368,580 people in control areas (<0.2 ppm fluoride). The water supply for 52% of the “high” fluoride population had average levels of ≥ 1 ppm (Heasman & Martin, 1962). Results indicated that there were no significant differences between areas with different fluoride levels in mortality due to coronary disease, angina, and other heart disease, as evidence by standard mortality ratios (SMRs). The second study (Hagan et al., 1954) examined 32 pairs of cities in the United States that contained 892,625 people in the high fluoride areas and 1,297,500 people in the control cities. A positive relationship between heart disease and water fluoridation was reported, but these authors did not adjust for a doubling of the members of this population over 75 years of age during the period of fluoridation under study (Jansen & Thomson, 1974). In addition, this study lacked statistical analysis and drew conclusions regarding trends that were not obvious from the data presented. The large variation in the presented data was not discussed. Doses of fluoride are difficult to estimate for large populations, however, because most people are potentially exposed to fluoride through a variety of sources, such as food, beverages, medicine, and dental products.

Pages 76-77: By contrast, a comparison of Bartlett & Cameron, two Texas towns with water supplies containing 8 and 0.4 ppm fluoride, respectively, found a significantly higher rate of cardiovascular system abnormalities in the town with the lower fluoride level (Leone et al., 1954). The authors attributed the finding of a significant result to the number of statistical tests that were conducted in the study. However, it is interesting to note that a study of 300 North Dakota residents who drank water containing 4-5.8 ppm and 715 people who drank water containing 0.15-0.3 ppm found a lower incidence of calcifications of the aorta in the high-fluoride group (Bernstein et al., 1966). Significant differences were found in the 45-54 year old males ($p < 0.05$), as well as in males aged 55-64 and 65+ years ($p = 0.01$). This effect was not due solely to differences in age distribution, because the incidence in the 55-64 year old – high fluoride group was lower than the incidence in the 45-54 year old, low-fluoride group. A crude analysis also found no association with milk and cheese consumption. Additional studies have suggested a role for fluoride in reducing cardiovascular disease. In a study of four towns in Finland, Luoma (1980) found that incidence of cardiovascular disease correlated negatively with water fluoride concentration. Taves (1978) likewise found that standard mortality ratios decreased to a greater extent in fluoridated cities from 1950-70 as compared to non-fluoridated control cities. Both studies, however, relied on population-summary information for disease rates. A mechanism for this potential reduction in cardiovascular disease could be the ability of fluoride to inhibit the calcification of soft tissue such as the aorta, as demonstrated in *in vitro* studies (Taves and Neumann, 1964; Zipkin et al., 1970).

Gastrointestinal effects (Page 78): While high levels of fluoride clearly can cause gastrointestinal irritation, it is unclear whether there are any GI effects of chronic exposure to fluoride in drinking water. GI tract disorders were not evaluated in the Bartlett-Cameron study of the effect of water containing 8 ppm fluoride (Leone et al., 1954).

The sole evidence of an effect comes from a study of 20 nonulcer dyspepsia patients at an outpatient clinic in India and 10 volunteers with out GI problems from the surgical clinic (Susheela et al., 1992). While none of the drinking water supplies of the controls had fluoride levels >1 ppm, the water supplies of 55% of the dyspepsia patients were at this level. In addition, all of dyspepsia patients and 30% of the controls had serum fluoride levels >0.02 ppm (mean of the dyspepsia group, 0.1 ppm); all of the dyspepsia patients and none of the controls had urine fluoride levels >0.1 ppm (mean 1.34 ppm). The study was compromised by small treatment size, undetermined total fluoride doses, undetermined nutritional status of the subjects, and a lack of statistical comparisons. In addition, the appropriateness of the control population was not clear.

Hematological effects (Page 79): The incidence of abnormal white blood cell counts was significantly higher in Bartlett Texas (8 ppm natural fluoride), than in Cameron, Texas (0.4 ppm fluoride). However, the study authors did not consider this finding as necessarily an effect of fluoride (Leone et al., 1954). No other significant hematological effects were observed.

Hepatic effects (Page 88): No studies were located regarding hepatic effects in humans after oral exposure to fluorine, hydrogen fluoride, or fluoride.

Renal effects (Page 89): One study was located in which ingestion of fluoride appeared to be linked with renal insufficiency (Lantz et al., 1987). A 32 year old man ingested 2-4 liters of Vichy water (a highly gaseous mineral water containing sodium, bicarbonate and approximately 8.5 mg/L of fluoride) every day for about 21 years. This exposure ended 4 years before his hospital admission. The patient also had osteosclerosis and a moderate increase in blood and urinary levels of fluoride. No teeth mottling was observed. The authors could not find factors, other than fluoride, related to his interstitial nephritis. No effect on the incidence of urinary tract calculi or the incidence of albuminuria was found in the Bartlett-Cameron study of people drinking water containing 8 ppm fluoride (Leone et al., 1954).

Endocrine effects (Page 89): Significant increases in serum thyroxine levels were observed in residents of North Gujarat, India with high levels of fluoride in the drinking water range of 1.0-6.53 mg/l; mean of 2.7 mg/L (Michael et al., 1996). No significant changes in serum triiodothyronine or thyroid stimulating hormone levels were found. Increases in serum epinephrine and norepinephrine levels were also observed. It is unclear if nutritional deficiencies played a contributing role to the observed endocrine effects.

Page 90: It is possible that the decreased level of bone resorption in the presence of fluoride, and the associated lowered serum calcium levels, would lead to secondary hyperparathyroidism in an attempt to maintain normocalcemia. To address this issue, rats were dosed with 3.3 mg/F/kg in drinking water for 46 weeks (Rosenquist et al., 1983). There were no changes in serum calcium or parathyroid hormone levels, and no increase in parathyroid activity.

Immunological and lymphoreticular effects (Page 90): A request to the American Academy of Allergy was made by the USPHS for an evaluation of suspected allergic reactions to fluoride used in the fluoridation of community water supplies (Austen et al., 1971). The response to this request included a review of clinical reports and an opinion as to whether these reports constituted valid evidence of a hypersensitivity reaction to fluoride exposure of types I, II, III, or IV (Austen et al., 1971), which are, respectively, anaphylactic or reagenic, cytotoxic, toxic complex, and delayed-type reactivity. The Academy reviewed the wide variety of symptoms presented (vomiting, abdominal pain, headaches, scotomata [blind or partially blind areas in the visual field], personality change, muscular weakness, painful numbness in extremities, joint pain, migraine headaches, dryness in the mouth, oral ulcers, convulsions, mental deterioration, colitis, pelvic hemorrhages, urticaria, nasal congestion, skin rashes, epigastric distress, and hematemesis) and concluded that none of these symptoms were likely to be immunologically mediated reactions of types I-IV. No studies were located that investigated alterations in immune response following fluoride exposure in humans.

Neurologic effects (Page 91): As discussed in developmental effects section, decreases in intelligence were reported in children living in areas of China with low levels of fluoride in the drinking water, as compared to matched groups of children living in areas with low levels of fluoride in the drinking water (Li et al., 1995a, Lu et al., 2000), but these studies are weak inasmuch as they do not address important confounding factors.

Reproductive effects (Page 92): There are limited data on the potential of fluoride to induce reproductive effects in humans following oral exposure. A meta-analysis found a statistically significant association between decreasing total fertility rate and increasing fluoride levels in municipal drinking water (Freni, 1994). Annual country birth data (obtained from the National Center for Health Statistics) for over 525,000 women aged 10-49 years living in areas with high fluoride levels in community drinking water were compared to a control population approximately 985,000

women) living in adjacent counties with low fluoride drinking water levels. The fluoride-exposed population lived in counties reporting a fluoride level of 3 ppm or higher in at least one system. The weighted mean fluoride concentration (county mean fluoride level weighted by the 1980 size of the population served by the water system) was 1.51 ppm (approximately 0.04 mg fluoride/kg/day), and 10.40% of the population was served by water systems with at least 3 ppm fluoride. The mean weighted mean fluoride concentration in the control population was 1.08 ppm (approximately 0.03 mg fluoride/kg/day). However, this meta-analysis relied on a comparison of two quite disparate data sets, inasmuch as the fluoridation population often did not correlate well with the population for whom health statistics was available. Furthermore, other studies have not found a similar correlation. Another study found significantly decreased serum testosterone levels in 30 men diagnosed with skeletal fluorosis and in 16 men related to men with fluorosis and living in the same house as the patient (Sushella and Jethanandani, 1996). The mean drinking water fluoride levels were 3.9 ppm (approximately 0.11 mg fluoride/kg/day), 4.5 ppm (0.13 mg fluoride/kg/day), and 0.5 ppm (0.014 mg fluoride/kg/day) in the patients with skeletal fluorosis, related men, and a control group of 26 men living in areas with low endemic fluoride levels. No correlations between serum testosterone and urinary fluoride levels or serum testosterone and serum fluoride levels were found. One limitation of this study is that the control men were younger (28.7 years) than the men with skeletal fluorosis (39.6 years) and the related men (38.7 years). In addition, the groups are small and potentially confounding factors are not well addressed.

Page 92: Studies that reported an increased incidence of Down's syndrome in areas of high fluoridation have not been replicated by several other investigations (Berry, 1958; Erickson et al., 1976; Needleman et al., 1974). No correlation was found between fluoridation and Down's syndrome incidence (corrected for maternal age) in a study of over 234,000 children in fluoridated areas and over 1,000,000 children in low-fluoride areas (Erickson et al., 1976). Ascertainment was based on birth certificates and hospital records, but was probably incomplete. Ascertainment was nearly complete in a study of over 80,000 children in fluoride areas and over 1,700,00 (sic) in low-fluoride areas, but no age-specific rates were reported (Needleman et al., 1974). Similarly, a study of the incidence of Down's syndrome in England did not find an association with the level of fluoride in water, but age-specific rates were not determined and tea was not taken into account as a source of fluoride (Berry, 1958).

Developmental effects (Page 94-95): Fluoride crosses the placenta in limited amounts and is found in fetal and placental tissue (Gedalia et al., 1961; Theuer et al, 1971). The available human data suggest that fluoride has the potential to be developmentally toxic at doses associated with moderate to severe fluorosis. The human and animal data suggest that the developing fetus is not a sensitive target of fluoride toxicity.

Analysis of birth certificates and hospital records for over 200,000 babies born in an area with fluoridated water and over 1,000,000 babies born in a low fluoride area found no difference in the incidence of birth defects attributable to fluoride (Erickson et al., 1976). Exposure to high levels of fluoride has been described together with an increased incidence of spina bifida (Gupta et al., 1995). The occurrence of spina bifida was examined in a group of 50 children aged 5-12 years living in an area of India with high levels of fluoride in the drinking water (4.5 – 8.5 ppm) and manifesting either clinical (bone and joint pain stiffness, and rigidity), dental, or skeletal fluorosis. An age- and weight-matched group of children living in areas with lower fluoride levels (≤ 1.5 ppm) served as a control group. Spina bifida was found in 22 (44%) of the children in the high fluoride area and in six (12%) children in the control group. This study did not examine the possible role of potentially important nutrients such as folic acid, however, and had other study design flaws.

A study by Li et al. (1995a) examined intelligence in children living in areas with high fluoride levels due to soot from coal burning. A group of 907 children aged 8-13 years were divided into four groups depending on the existence and severity of dental fluorosis; 20-24 children in each age group for each area were examined for intelligence. A significant decrease in IQ was measured in children living in the medium- (mean IQ of 79.7) and severe- (mean of 80.3) fluorosis areas, as compared to the children living in the non- (mean of 89.9) or slight- (mean of 89.7) fluorosis areas. More children with IQs of <70 and 70-79 and fewer children with IQs of 90-109 and 110-119 were found in the medium- and severe-fluorosis areas than in the non- or slight-fluorosis areas. No information on exposure levels were provided; the mean urinary fluoride levels were 1.02, 1.81, 2.01 and 2.69 mg/L in the non-, slight-, medium-, and severe-fluorosis areas, respectively. Numerous potentially confounding variables were not mentioned in this study, however, which raised questions regarding the validity of the study's findings. A study by Lu et al. (2000) also examined exposure to high fluoride levels in the drinking water (3.15 mg/L) were examined for intelligence. The test results were compared to a group of 58 children with similar social, education, and economic backgrounds who lived in an area with low fluoride levels in water (0.37 mg/L). A significant decrease in IQ was observed in the high fluoride area (mean IQ of 92.27) as compared to the control group (103.05). Additionally, there was a significantly higher number of children from the high exposure area with IQ scores of <70 (retarded) and 70-

79 (borderline retarded) than in the control group. A significant inverse relationship between urinary fluoride levels and IQ was also found. Nevertheless, because this study relied on small groups and presented scant discussion of numerous potential confounders, the strength of its conclusions are questionable.

NHS Centre for Reviews and Dissemination, University of York. (2000). A systematic review of public water fluoridation. York, UK: York Publishing Services Ltd.

Various outcomes addressed include: Alzheimer's disease, impaired mental functioning, primary degenerative dementia, anemia during pregnancy, age at menarche, congenital malformations, Downs' syndrome, infant mortality, sudden infant death syndrome, all cause mortality, IQ, mental retardation, goiter.

Page xiii, xiv: A total of 33 studies of the association of water fluoridation with other possible negative effects were included in the review. Interpreting the results of studies of other possible negative effects is very difficult because of the small numbers of studies that met inclusion criteria on each specific outcome and poor study quality. A major weakness of these studies generally was failure to control for any confounding factors.

Overall, the studies examining other possible negative effects provide insufficient evidence on any particular outcome to permit confident conclusions. Further research in these areas needs to be of a much higher quality and should address and use appropriate methods to control for confounding factors.

Page 63: Interpreting the results of other possible negative effects is very difficult because of the small number of studies that met inclusion criteria on each specific outcome, the study designs used and the low study quality.

The quality of the research on these topics was generally low, evidence level C (mean of 2.7 out of 8 on validity assessment). Given that all studies are from the lowest level of evidence with the highest risk of bias, the conclusions should be treated with caution.

A major weakness of these studies generally was the lack of control for any possible confounding factors, many of which were highlighted by the study authors. If the populations being studied differed in respect to other factors that are associated with the outcome under investigation then the outcome may differ between these populations leading to an apparent association with water fluoride level. What is clear is that any further research in these areas needs to be of a much higher quality and should address and use appropriate methods to control for confounding factors.

Overall the studies examining other possible negative effects provide insufficient evidence on any particular outcome to reach conclusions. Very few of the possible adverse effects studied appeared to show a possible effect. High quality research that takes confounding factors into account is needed.

National Research Council. (1993). Health effects of ingested fluoride. Washington, D.C.: National Academy Press.

Effects of Fluoride on the Renal System (Page 7-8): Renal excretion is the major route of elimination for inorganic fluoride from the body. As a result, kidney cells are exposed to relatively high fluoride concentrations, making the kidney a potential site for acute fluoride toxicity. Animal studies have shown that very high water fluoride concentrations of 100-380mg/L can lead to necrosis of proximal and renal tubules, interstitial nephritis, and dilation of renal tubules. However, human epidemiological studies have found no increase in renal disease in populations with long-term exposure to fluoride at concentrations of up to 8mg/L of drinking water.

The subcommittee concludes that available evidence shows that the threshold dose of fluoride in drinking water for renal toxicity in animals is approximately 50 mg/L. The subcommittee therefore believes that ingestion of fluoride at currently recommended concentrations is not likely to produce kidney toxicity in humans.

Effects of Fluoride on the Gastrointestinal System (Page 8): In the acid environment of the stomach, fluoride and hydrogen ions can combine to form hydrogen fluoride, which, at sufficiently high concentrations, can be irritating to the mucous membranes of the stomach lining. Experimental studies with several animal species have shown dose-dependent adverse effects, such as chronic gastritis and other lesions of the stomach, at fluoride concentrations of 190 mg/L and higher. Reports of gastrointestinal effects in humans often involve workers exposed to unknown concentrations of fluoride in the workplace, so that the contribution of fluoride exposure to the risk of adverse health effects is unknown. The subcommittee noted that these workers could also be exposed to other toxic substances present in the work environment. There have been few studies of the gastrointestinal effects of fluoride at low concentrations.

The subcommittee concludes that the available data show that the concentrations of fluoride found in drinking water in the United States are not likely to produce adverse effects in the gastrointestinal system.

Effects of Fluoride on Hypersensitivity and the Immune System (Pages 8-9): Few animal and human data on sodium fluoride-related hypersensitivity reactions are found in the literature. In animal studies, excessively high doses, inappropriate routes of administration of fluoride, or both were used. Thus, the predictive value of those data, in relations to human exposures at accepted exposure levels, is questionable. Reports of hypersensitivity reactions in humans resulting from exposure to sodium fluoride are mostly anecdotal.

The literature pertaining to immunological effects of fluoride is limited. Although direct exposure to high concentrations of sodium fluoride in vitro affects a variety of enzymatic activities, the relevance of the effects in vivo is unclear. Standardized immunotoxicity tests of sodium fluoride at relevant concentrations and routes of administration have not been conducted. The weight of evidence shows that fluoride is unlikely to produce hypersensitivity and other immunological effects.

Effects of Fluoride on Reproduction (Page 9): There have been reports of adverse effects on reproductive outcomes associated with high levels of fluoride intake in many animal species. In most of the studies, however, the fluoride concentrations associated with adverse effects were far higher than those encountered in drinking water. The apparent threshold concentration for inducing reproductive effect was 100 mg/L in mice, rats, foxes and cattle; 100-200 mg/L in minks, owls, and kestrels; and over 500 mg/L in hens.

Based on these findings, the subcommittee concludes that the fluoride concentrations associated with adverse reproductive effects in animals are far higher than those to which human populations are exposed. Consequently, ingestion of fluoride at current concentrations should have no adverse effects on human reproduction.

Genotoxicity (Pages 9-10): Fluoride has been tested extensively for its genotoxicity. It does not damage DNA or induce mutations in microbial systems, but it has produced mutations and chromosomal damage in several in vitro tests with mammalian cells. Sodium fluoride, in particular, inhibits protein and DNA synthesis and has been reported to cause chromosomal aberrations in human cells. The lowest effective dose in these cell-culture studies was a fluoride concentration of approximately 10 $\mu\text{g}/\text{mL}$, whereas the normal concentration in human plasma is 0.02-0.06 $\mu\text{g}/\text{mL}$, even in areas where drinking water is fluoridated, which means that there is a large margin of safety.

Sodium fluoride and other fluoride salts also have been tested for genotoxicity in the fruit fly *Drosophila*, as well as in mice and rats. The subcommittee's review of the results of these in vivo studies was inconclusive, however, because of differences in protocols and insufficient detail to support a thorough analysis. There are no published studies on the genetic or cytogenetic effects of fluoride in humans.

The subcommittee concludes that the genotoxicity of fluoride should not be of concern at the concentrations found in the plasma of most people in the United States.

Committee to Coordinate Environmental Health and Related Programs, USPHS. (1991). Review of fluoride: Benefits and risks: Report of the subcommittee on fluoride of the EHPC. Public Health Service: Department of Health and Human Services.

Page 3, executive summary: The PHS subcommittee undertook a comprehensive review of the possible association between fluoride exposure and various adverse health outcomes. The report concluded that there is a lack of evidence of associations between levels of fluoride in water and birth defects or problems of the gastro-intestinal, genito-urinary, and respiratory systems.

Summary of studies investigating the effects of fluoride on the renal system (Page 65): The kidney is a potential target organ for chronic fluoride toxicity because the healthy kidney removes fluoride from the blood much more readily than it removes other halogens. The fluoride ion is filtered from plasma in the glomerular capillaries into the urinary space by Bowman's capsule; with a variable degree of tubular reabsorption by diffusion of the hydrogen fluoride molecule. Renal fluoride clearance increases with age, with a peak at about 50 years, but the mean renal clearance was about twice as high for persons from an area with fluoridated drinking water as for those from an area with water low in fluoride. Serum fluoride concentrations above about 30 $\mu\text{mol}/\text{L}$ cause renal concentrating defects in rats, dogs, and humans. Decreased fluoride clearance may occur among persons with impaired renal function, but the overall health significance of reduced fluoride clearance is uncertain, with no cases of symptomatic skeletal fluorosis being reported among persons with impaired renal function. Several epidemiological investigations have found no human kidney disease from long-term non-occupational exposure to fluoride with drinking water up to 8 mg/L.

Studies investigating the effects of fluoride on the gastrointestinal system (Page 66): All the soluble, fluoride releasing compounds except monofluorophosphate form hydrogen fluoride when mixed with hydrochloric acid in the stomach. At optimal levels of fluoride in the water, however, gastrointestinal effects are not a problem. There are no reports of gastrointestinal problems in populations with non-occupational fluoride exposure.

Studies investigating the effects of fluoride on the reproductive system (Page 67): It is not yet clear whether fluoride is essential for reproductive performance. Several species are sensitive to fluoride levels higher than those normally encountered, such that their fertility and reproductive performance is impaired. The association of adverse reproductive effects of fluoride exposure in humans has not been adequately evaluated.

Teratologic and developmental effects (Page 69): Fluoride crosses the placenta and is incorporated in tissues of the developing conceptus. Limited animal data report defects of the teeth in offspring of mothers exposed to high dose levels of fluoride. In humans, studies in areas of India and Africa with high levels of naturally fluoridated water showed no increase in birth defects but signs of skeletal fluorosis became evident during childhood. No association was observed between birth defects and fluoridation of community water supplies based on the birth defect registry of the greater metropolitan area of Atlanta, Georgia. About 30 years ago, an investigator linked an excess of Down syndrome, a genetic disorder, to fluoridation, but the results of three later studies conducted by other investigators with a fuller ascertainment of cases did not confirm that finding.

Studies investigating the hypersensitivity and immunologic effects of fluoride (Pages 69-70): The literature contains minimal animal and human data on sodium fluoride-related hypersensitivity reactions. In animal studies, investigators often used excessively high doses, inappropriate routes of administration, or both (Lewis & Wilson, 1985; Jain & Susheela, 1987). Consequently, the predictive value of these data, as they relate to human exposures at accepted exposure levels, is questionable. Reports of human hypersensitivity reactions resulting from exposure to sodium fluoride are scattered and largely anecdotal (Razak & Latifah, 1988; Modly & Burnett, 1987; Richmond, 1985; Arnold et al., 1960). The most common responses observed included dermatitis, urticaria, inflammation of the oral mucosa, and gastrointestinal disturbances. Hypersensitivity reaction associated with dental preparations were mild to moderate in severity and appeared to resolve completely with discontinuation of the product (Adair, 1989). It was reported that these reactions were caused by sodium fluoride or by alcohol, dyes, or flavoring agents in the products.

Waldbott (1962) reported that the ingestion of 1 mg/L fluoride in water produced numerous symptoms, which included gastrointestinal distress and joint pains. These symptoms were also reported in a few patients when a daily dose of 20 mg or more was administered to patients as treatment for bone conditions (Shambaugh & Sundar, 1969; Rich et al., 1964). These symptoms are not believed to be caused by chronic intake of fluoride at any dose level, let alone at the low fluoride exposure levels cited by Waldbott. These findings have been dismissed for the following reasons: 1) insufficient clinical and laboratory evidence of allergy or intolerance to fluorides used in the fluoridation of community water, and 2) no evidence of immunologically mediated reactions in a review of the reported allergic reactions (Austen et al., 1971).

Waldbott (1978) proposed that a specific skin manifestation called Chizzola maculae could be caused by airborne fluorides. Waldbott and Steinegger (1973) claimed that this skin lesion was caused by drinking fluoridated water, but could not offer evidence to support this hypothesis. Additional claims (Waldbott & Ceciloni, 1969) attributed the development of these discrete skin lesions to fluoride exposure in 10 of 32 persons living near fertilizer plants in Ontario, Canada, and Iowa, and near an iron foundry in Michigan. The evidence for Chizzola maculae as a result of exposure to fluoride has been reviewed extensively by several investigators (Hodge & Smith, 1977), who concluded that the evidence was circumstantial and unsupported by field surveys.

The literature pertaining to immunologic and immunomodulation effects of fluoride is limited. Although direct exposure to high concentrations of sodium fluoride *in vitro* affects a variety of enzymatic activities (Okada & Brown, 1988; Salesse & Garnier, 1984; Takanaka & O'Brien, 1985; Alm, 1983; Mizuguchi et al., 1989; Mircevova et al., 1984; Carr et al., 1985; O'Shea et al., 1987), the *in vivo* relevance of these observations is unclear. Standardized immunotoxicity testing of sodium fluoride at relevant concentrations and routes of administration has not been conducted.

Genotoxicity (Page 71): Genotoxicity studies of fluoride, which are highly dependent on the methods used, often show contradictory findings. The most consistent finding is that fluoride has not been shown to be mutagenic in standard tests in bacteria (Ames test). In some studies with varying methodologies, fluoride has been reported to induce mutations and chromosome aberrations in cultured rodent and human cells. The genotoxicity of fluoride in humans and animals is unresolved despite numerous studies.

International Programme on Chemical Safety. (1984). Environmental health criteria 36: Fluorine and fluorides. Geneva, Switzerland: World Health Organization.

Effects on Kidneys (Pages 83-84): Although there are no reports of fluoride-induced chronic renal disorders in healthy individuals, several studies have dealt with the possible influence of fluoride on people with manifest kidney diseases. In patients with kidney failure, fluoride excretion is decreased, and the ionic plasma fluoride concentration is higher than the normal (Juncos & Donadio, 1972; Berman & Taves, 1973; Hanhijärvi, 1974). The capacity of the skeleton to store fluoride may provide a sufficient safety margin (Hodge & Smith, 1954; Hodge & Taves, 1970). On the other hand, it seems also plausible that an increased plasma fluoride concentration may result from fluoride liberation from the bone resorption processes involved in certain kidney diseases. Patients with diabetes insipidus may absorb excess amounts of fluoride because of the large quantities of fluoride ingested.

Patients with chronic renal failure who are dialysed with fluoridated water receive an additional load of fluoride from the dialysate. In comparison with the average gastrointestinal uptake, the fluoride absorption increases by 20 – 30-fold during a single pass of dialysis. Thus, raised ionic fluoride levels in plasma have been reported (Taves et al., 1965; Fournier et al., 1971). However, aluminum is currently viewed as the major causative factor associated with both encephalopathy and bone disease in dialysed kidney patients (Platts et al., 1997). The entire subject of water suitable for dialysis was considered by a joint working party set up in 1979 by the Australasian Society of Nephrology and the Australian Kidney Foundation Dialysis and Transplant Committee. Its report suggested a maximum limit of 0.2 mg fluoride/liter in the dialysate (Victoria Committee, 1980).

Teratogenicity (Pages 85-86): The results of a recent study suggest that fluoride may indeed exert effects on fetal growth: babies, whose mothers had received fluoride tablets during pregnancy, were somewhat heavier and slightly longer at birth, and prematurity was much less frequent, compared with control groups (Glenn et al., 1982).

Rapaport (1956, 1959, 1963) reported an augmented frequency of Down's syndrome with increasing water fluoride concentrations. In the first study (Rapaport, 1956), data were examined in relations to the place of birth, not to the place of residence of the mother. Subsequent papers (Rapaport, 1959, 1963) gave frequency figures for Down's syndrome of only 0.24 – 0.40 per 1000 births in low-fluoride areas and 0.70 – 0.80 in high-fluoride areas. His study comprised cases of Down's syndrome registered in specialist institutions in four American states and on birth and death certificates in a fifth state. Information was gathered for the years 1950-56. Many cases may not have been detected, because they were cared for at home.

Berry (1962) examined Down's syndrome in certain English cities and did not find any differences between areas with low (< 0.2 mg/liter) and high (0.8 - 2.6 mg/liter) fluoride levels in the drinking-water. The rates were 1.58 and 1.42 cases per 1000 births, respectively. The English custom of tea-drinking was not taken into account, and the data were not presented in age-specific groups. Needleman et al., (1974) recorded all children born alive with Down's syndrome among Massachusetts residents during the period 1950-66. The number found was 1.5 per 1000 births in both low-fluoride and fluoridated areas, but age-specific rates were not given. Erickson et al. (1976) and Erickson (1980) did not find any difference in the incidence of Down's syndrome between fluoridated and low-fluoride areas, on the basis of birth certificates. However, the considerable material gathered in this way may only have covered about a half of the real number of children born with Down's syndrome. Berglund et al. (1980) related the incidence in Sweden during 1968-77 to mean water fluoride content of the areas where the mothers were living. Virtually all cases of Down's syndrome were probably recognized and the incidence rates per 1000 births during the period were found to range from 1.32 to 1.46. The material was divided into groups according to the maternal age below or above 35 years of age. No influence of fluoride on the incidence of Down's syndrome was seen.

Effects on Mortality Patterns (Pages 86-87): A report stated that the mortality rate from heart diseases had nearly doubled from 1950 to 1970 following the introduction in 1949 of fluoridation of the drinking-water in Antigo, Wisconsin, a little town with only 9000 inhabitants (Jansen & Thomsen, 1974). The report did not adjust for the fact that the number of people ages 75 years or more had also doubled in this period. Subsequently, epidemiologists from the American National Heart and Lung Institute did not find any correlation between deaths due to heart diseases and water fluoridation in Antigo (US NIH, 1972).

Several epidemiological studies, some of them very large, have not revealed any indications that fluoride in drinking-water increases the mortality rate from heart diseases (Hagan et al, 1954; Schlesinger et al, 1956; Heasman & Martin, 1962; Luoma et al., 1973; Bierenbaum & Fleischman, 1974; Erickson, 1978; Rogot et al., 1978; Taves, 1978). In fact, some of these studies point to the beneficial effects of fluoride in heart diseases (Heasman & Martin, 1962; Luoma et al., 1973; Taves, 1978). Considering reports indicating that fluoride may reduce soft tissue

calcification such as atherosclerosis (Leon et al., 1954, 1955; Heasman & Martin, 1962; Taves & Neuman, 1966; Bernstein et al., 1966; Zipkin et al., 1970), it seems of value to encourage further research on the relationship between fluoride and cardiovascular diseases.

Allergy, Hypersensitivity, and Dermatological Reactions (Pages 87-88): In 1971, the American Academy of Allergy examined the literature on alleged allergic reactions to fluoride: (Feltman, 1956; Feltman & Kosel, 1961; Burgstahler, 1965; Waldbott, 1965; Shea et al., 1967). The conclusions of the Executive Committee were (Austen et al., 1971): “The review of the reported allergic reactions showed no evidence that immunologically mediated reaction of the types I-IV had been presented. Secondly, the review of the cases reported demonstrated that there was insufficient clinical and laboratory evidence to state that true syndromes of fluoride allergy or intolerance exists.” As a result of this review, the members of the Executive Committee of the American Academy of Allergy adopted unanimously the following statement: “There is no evidence of allergy or intolerance to fluorides as used in the fluoridation of community water supplies.”

Since 1971, only in a few reports in the allergy literature have allergic reactions been suspected to be connected with fluoride exposure. Petraborg (1974) described seven patients with various symptoms appearing a week after the introduction of water fluoridation. Grimbergen (1974) using a double blind provocation test reported on a patient showing allergic reactions to fluoridated water. Waldbott (1978) reviewed previous reports.

However, no animal or laboratory studies have indicated the existence of fluoride allergy or fluoride intolerance, and no plausible mechanism for such allergic reactions has been suggested. Thus, the allergenic effects of fluoride remain unproven.

Other Reviews

(examples of municipal or territorial reviews of the water fluoride issue)

Lepo, J.E. & R.A. Snyder (2000, May). (On-line). Impact of Fluoridation of the Municipal Drinking Water Supply: Review of the Literature. Prepared for the Escambia County Utilities Authority. The Center for Environmental Diagnostics and Bioremediation.

Mutagenicity (Page 15): There have been several reports of mutagenicity of HF or NaF on plants, *Drosophila* (Fruit fly), and mammals; and several reports of the lack of mutagenicity in similar organisms have likewise been published (studies cited in U.S. Environmental Protection Agency, 1988). The International Agency for Research on Cancer (1982) describes the lack of mutagenic effects on the bacterium *Salmonella typhimurium* (the Ames Test, which is a standard screen for mutagenic materials) and the yeast *Saccharomyces cerevisiae*.

Many other studies typically employ in vitro tissue culture into which fluoride is introduced in the culture medium. For instance, a series of studies by Tsutsui and coworkers (1984a; 1984b; 1984c) found evidence for DNA damage in cultured human or Syrian hamster cells including both chromosome aberrations and unscheduled DNA synthesis. Tsutsui et al. (1984c) point out that genotoxicity has been demonstrated in many in vitro studies but in a few in vivo studies, and that concentrations employed in such studies are often as high as 10,000 times that of typical environmental exposure. Fluoride ion at these levels inhibits many enzymes, and in such in vitro studies it may interfere with enzymes involved in DNA repair or replication rather than by direct interaction with the DNA itself.

Brain Effects (Pages 15 – 16): Varner et al. (1993) published a study of male rats treated with AlF_3 – a complex of aluminum and fluoride – at 0.5, 5.0 and 50 ppm in their drinking water. They found significant effects in the lowest concentration rather than at the higher two concentrations. They subsequently refined the study (Varner et al., 1998) with equivalent levels of NaF to deliver the same F as in the AlF_3 complex. In these experiments the AlF_3 -exposed rats showed higher mortality and brain tissue anomalies relative to the NaF or control group rats. To our knowledge, the work described in these papers has been cited almost exclusively on the anti-fluoridation websites, in the journal *Fluoride*, and in the publications of Varner and coauthors. Since other workers in the field have not responded by either citing or commenting on the work to either support or refute their findings, the work of Varner and colleagues lacks peer response from the scientific community. At present there is insufficient independent information to either confirm or deny these findings.

Other Adverse Health Effects (Page 16): In contrast to the above dearth of scientific acknowledgement of the Varner publications, we were able to find many independent studies conducted both before and after the initiation of supplemental fluoridation in which there were no changes in death rates from cancer, heart disease, intracranial lesions, nephritis, cirrhosis, or from all causes (several of these are cited in Richmond, 1985). The issue of adverse

health effects has been reviewed in a *Scientific American* article by Doyle (1996). Several investigations address whether fluoride might adversely affect health in medically compromised mammals or interact with conditions such as renal insufficiency or diabetes. For instance Dunipace and coworkers (1996) found that diabetic rats retained more fluoride than their non-diabetic counterparts; however, they discovered no adverse effects on the physiological, biochemical, or genetic variables monitored.

There is no credible evidence for acute or chronic hypersensitivity (allergic response) among the billions of consumers of fluoride-rich beverage, tea, which provides 1 – 4 mg fluoride per cup (Richmond, 1985). The treatment of several hundred multiple myeloma patients with daily doses of 50 – 100 mg fluoride for up to 70 months resulted in no significant effect on the progress of the disease; nor were there side effects from the fluoride exposure that were different from side effects observed from the placebo controls (Harley and Schilling, 1972; Kyle et al., 1975).

These and many other instances of a lack of even a correlation between fluoride exposure and adverse health or physiological effects is further emphasized when one considers the general good health and longevity of millions of residents in the United States who live for several generations in areas with natural fluoridation of drinking water at 2 to 10 mg/L (Dean, 1936; Dean, 1938; Shaw, 1954; Richmond, 1985; Public Health Service, 1991; see also, National Academy Press, 1999 and papers cited therein; also on the Internet at <http://www.nap.edu/books/0309063507/html/288.html>).

Locker, David. (1999). Benefits and risks of water fluoridation. An update of the 1996 federal-provincial sub-committee report. Prepared under contract for the Public Health Branch, Ontario Ministry of Health, First Nations Inuit Health Branch, Health Canada. University of Toronto: Community of Dental Health Services Research Unit, Faculty of Dentistry.

Child Development (Page 53): Early studies of child development in fluoridated and non-fluoridated communities focused on physical health. No differences were documented with respect to body processes, blood chemistry, vision, hearing or any other general health parameter.

More recent studies have focused on intellectual development. Two conducted in China claimed to have found differences in IQ between children exposed to differing levels of fluoride. Although both fell outside the inclusion criteria they were reviewed to illustrate the flaws in this research. The first (Zhao et al., 1996) compared the IQ of children in one village where the water supply contained 4 ppm fluoride and one village where the concentration of fluoride was 0.9ppm. The mean IQ of random samples of children was 105 in the former and 98 in the latter, a statistically significant difference. In both villages, children of parents with a higher education had a higher IQ. However, analysis of mean IQ scores adjusting for the confounding effect of parental education was not undertaken. Nor was the effect of other potential confounders taken into account. The second study compared the IQ scores of children from four areas with differing levels of dental fluorosis. The source of fluoride was not water but soot due to coal burning. The Dental Fluorosis Index scores varied from 0.4 to 3.0. The latter is seen in areas fluoridated to approximately 8ppm. Significant differences were observed in the IQ scores of children living in non-fluorosis and severe fluorosis areas (90 vs. 80, respectively). It is not clear if the children examined in each area were randomly sampled. Nor was any attempt made to control for potential confounders or the effects of other pollutants present in soot from coal.

Immune Function (Page 53): No studies of the effect of water fluoridation on immune function were published between 1994 and 1999. However, a review paper (Challacombe, 1996) examined studies of fluoride and immune response published prior to 1992 and found no support for the suggestions that fluoride affects immunity.

Report of the expert panel for water fluoridation review. (March 1998). City of Calgary, and Calgary Regional Health Authority: Appointed by the Standing Committee on Operations and Environment.

Page 30, summary majority opinion: From the perspective of epidemiology and toxicology, the available scientific literature has not substantiated the claims that water fluoridation was a factor in other adverse health effects. The results found in the literature have not eliminated the need for further research. Carefully designed studies, which take into account total fluoride intake and all other relevant factors, are required. There is no need for or value in further studies which attempt to relate water fluoridation per se to adverse health effects.

Although there is considerable literature on the effects of fluoride, many of these studies were related to high dose toxicity or to the effects of high therapeutic doses. Studies at these high levels were not considered relevant by the Panel.

The Lord Mayor's taskforce on fluoridation – final report. (1997). Brisbane, Australia: Brisbane City Council.

Renal and Gastrointestinal Effects (Page 52): The kidney is a site for potential toxicity because this organ is exposed to relatively high concentrations of fluoride as approximately 50% of ingested fluoride is cleared from the body by the kidneys. The study found no evidence to suggest that water fluoridation was associated with an increased risk of renal disease.

Water used by kidney dialysis patients for haemodialysis after purification by reverse osmosis, has been reported to contain significantly higher levels of fluoride than commercially prepared peritoneal dialysis fluid (Bello et al., 1990). The authors suggested that the common usage of reverse osmosis to purify water for dialysis meant that in areas with fluoridated water, dialysis patients might, inadvertently, be exposed to too much fluoride. In the US, an outbreak of acute illness occurred in 12 of 15 patients treated in one dialysis room, compared with no cases in 17 patients treated in the second room at the same unit. The cases had unusually high serum fluoride levels and the cause of this was traced to a temporary deionization system (Arnow et al., 1994).

Allergy (Page 52): Cases of asthma have been reported in adults exposed to fluoride in an occupational setting (Kongerud et al., 1994), and in children living near an aluminum smelter and exposed to air containing fluoride. However, there appeared to be no confirmed cases of allergic reactions following water fluoridation.

Consumption of tea, which contains high levels of fluoride, was not commonly associated with allergic reaction. Nevertheless, a small proportion of the public were convinced that they have suffered an allergic reaction caused by fluoride in the water.

Sudden Infant Death Syndrome (SIDS) (Page 53): A number of studies have examined whether water fluoridation might be linked with a higher level of SIDS. Although a comparison of SIDS rates in the Australian capitals (Walker, 1992) claimed that Hobart with the longest history of fluoridation had the highest rates, followed by Canberra, while the rates were lowest in Melbourne which was non-fluoridated, there are likely to be many other differences between these cities that could explain the variation in SIDS rates. In conclusion, the study found no scientific evidence to suggest that fluoridation might increase the risk of SIDS.

Reproductive Effects and Fertility (Page 53): A single study has attempted to relate fertility to exposure to fluoride in humans (Freni et al., 1994). A few occupational studies have suggested that workers in certain industries, who are exposed to fluorides amongst other potentially hazardous compounds, experienced a range of adverse health effects including reduced testosterone levels in men and menstrual irregularities and spontaneous abortion in women. In all of these studies it was impossible to ascribe an effect to fluoride with any certainty because of the parallel exposure to a range of other compounds. In conclusion, the review found no reliable evidence to support an association between exposure to fluoridated water and any adverse reproductive effects.

Genetic Defects (Page 53): A number of small studies have suggested an association between fluoride and congenital malformation or Down syndrome. Earlier studies had suggested a link but have since been shown to be flawed, and more recent studies have not supported this hypothesis (IARC, 1982; NHMRC, 1985; PHC, 1993). The review concluded that there was no strong scientific evidence to support such an association.

Thyroid and Brain Function (Page 54): In a study of 26 adolescents aged 13-15 consuming water containing fluoride at 3 ppm, a level higher than in fluoridated water, there was no effect on thyroid function (Baum et al., 1981). Other studies have considered thyroid function in patients treated with high doses of fluoride. In one study of patients treated for osteoporosis with 60 mg of Sodium Fluoride per day, some patients experienced joint pain and gastrointestinal effects but no changes in renal, bone marrow or thyroid function (Hasling et al., 1987). Exposure to fluoride in patients treated for osteoporosis would be considerably greater than that associated with consumption of fluoridated water.

Studies in animals have reported both the presence and absence of adverse effects of high levels of fluoride on thyroid function. A review of fluorine and thyroid function concluded that the published data did not support the view that fluoridated water had an adverse effect on the thyroid (Burgi et al., 1984). Another concern expressed is that fluoridated water may be associated with Alzheimer's disease because of contamination with aluminum.

However, on the basis of current evidence, aluminum exposure has not been clearly established as a causal factor in the development of Alzheimer's disease. There is an alleged link between fluoride intake and both brain function impairment and a protective effect. The scientific findings, however, are not consistent.

Other Conditions (Page 54): There is an alleged link between fluoridated water consumption and a number of other adverse health effects including ageing, immune system damage, and magnesium/calcium deficiency. However, the review could find no reliable scientific evidence of an increased risk of these conditions.

Cardiovascular Disease (Page 54): A number of studies have shown conflicting results in relation to a possible beneficial link between fluoride and the incidence of cardiovascular disease. Some studies have shown an apparent decrease in the prevalence of cardiovascular disease in areas with higher fluoride levels, while others have shown no link. There is insufficient evidence to establish a causal link.

Natick Fluoridation Study Committee. (1997). Should Natick fluoridate?: A report to the town and Board of Selectmen. (On-line).

Page 3, findings

- Fluoride adversely effects the central nervous system, causing behavioral changes and cognitive deficits. These effects are observed at fluoride doses that some people in the US actually receive.
- There is good evidence that fluoride is a developmental neurotoxicant, meaning that fluoride effects the nervous system of the developing fetus at doses that are not toxic to the mother. The developmental neurotoxicity would be manifest as lower IQ and behavioral changes.
- Some adults are hypersensitive to even small quantities of fluoride, including that contained in fluoridated water. At lease one such person is a Natick resident.
- The impact of fluoride on human reproduction at the levels received from environmental exposures is a serious concern. A recent epidemiology study shows a correlation between decreasing annual fertility rate in humans and increasing levels of fluoride in drinking water.
- Fluoride inhibits or otherwise alters the actions of a long list of enzymes important to metabolism, growth, and cell regulation.
- Sodium fluorosilicate and fluorosilicic acid, the two chemicals Natick intends to use to fluoridate the water supply, have been associated with increased concentrations of lead in tap water and increased blood lead levels in children, based on case reports and a new, as-yet-unpublished study.